ECZEMA

CHI Formulary Development Project

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- September 2023

To the CHI Original Eczema Clinical Guidance- Issued February 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

AAD	American Academy of Dermatology
AD	Atopic Dermatitis
AE	Atopic Eczema
CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
EASI	Eczema Area and Severity Index
EMA	European Medicines Agency
ETFAD	European Task Force on Atopic Dermatitis
FDA	Food and Drug Administration
GoR	Grade of Recommendation
HTA	Health Technology Assessment
IDF	Insurance Drug Formulary
JAKi	Janus Kinase Inhibitor
LoE	Level of Evidence
mAB	Monoclonal Antibody
N/A	Not Available
PA	Prior Authorization
PDE-4i	Phosphodiesterase-4 Inhibitor
SC	Subcutaneous
TCI	Topical calcineurin inhibitor
TCS	Topical Corticosteroid

Executive Summary

Eczema is classified as an inflammatory skin condition, and leads to various manifestations such as itchiness, dry skin, rashes, scaly patches, blisters, and, in some cases, skin infections. Among the array of symptoms, itchy skin stands out as the prevailing and most frequently experienced sign of eczema. Atopic dermatitis (AD) is the most common form of eczema, and the two terms are often used interchangeably[1].

Eczema, also referred to as atopic dermatitis, represents the prevalent type of dermatitis. Both genetic predisposition and environmental influences are believed to contribute to its development. Although more frequently observed in children, eczema can also manifest in adults[2].

Eczema is a significant condition that impacts approximately 20% of children and up to 10% of adults. This condition carries a substantial burden of morbidity and imposes considerable costs on both affected individuals and healthcare services[3].

The prevalence of AD among adults in various provinces of Saudi Arabia varies, ranging from 6% to 13%[4].

The primary treatment objectives of eczema are to understand the nature of the condition, avoid trigger factors, alleviate itching and diminish inflammation, cultivate realistic expectations regarding eczema management, gain insight into the pros and cons of different treatment options and decrease the frequency and intensity of flare-ups[5].

CHI issued eczema clinical guidance after thorough review of renowned international and national clinical guidelines in February 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Eczema clinical guidance and seeks to offer guidance for the effective management of Eczema. It provides an **update on the Eczema Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, by being the addition of three new SFDA registered drugs **Baricitinib**, **Upadacitinib** and **Tralokinumab** and one new non-SFDA registered drugs: **Delgocitinib**. There is also the Guidelines of care for the management of atopic dermatitis in adults with topical therapies **(2023)**, an update of the American academy of dermatology (2014). Moreover, **new guidelines are added to the report** such as the English Version of Clinical Practice Guidelines for the Management of Atopic Dermatitis **2021**, the Japanese guidelines for atopic dermatitis **2020**, the European task force on atopic dermatitis position paper:

treatment of parental atopic dermatitis during preconception, pregnancy, and lactation period, the German S1 guidelines for the diagnosis and treatment of perianal dermatitis (anal eczema) (**2020**), the Management of Atopic Dermatitis in Adults in Saudi Arabia: Consensus Recommendations from the Dermatological Expert Group (**2022**), the Brazilian Society of Dermatology consensus on the therapeutic management of atopic dermatitis (**2019**), the diagnosis and management of moderate to severe adult atopic dermatitis published jointly by the Italian Society of Dermatology and Venereology (SIDeMaST), the Italian Association of Hospital Dermatologists (ADOI), the Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC), the Italian Society of Allergological, Environmental and Occupational Dermatology (SIDAPA) (**2018**), the European guideline (EuroGuiDerm) on atopic eczema: part I – systemic therapy **(2022),** and finally the European guideline (EuroGuiDerm) on atopic eczema – part II: non-systemic treatments and treatment recommendations for special AE patient populations **(2022).**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to include the SFDA registered drug **Baricitinib** (OLUMIANT ®), **Upadacitinib** (RINVOQ®) and **Tralokinumab** (ADTRALZA®) in the CHI formulary while changing some related prescribing edits to previously listed drugs in the February 2020 CHI report which are: Azathioprine, Cefalexin, Ciclopirox, Cyclosporin, Fluconazole, Fusidic acid, Itraconazole, Methotrexate, Mupirocin calcium, Mycophenolate, Pimecrolimus do not need "Prior Authorization (PA)" as a prescribing edit: Dupilumab does need "PA" as a prescribing edit: This drug should be given for patients older than 6 months of age with moderate to severe AD in whom it is difficult to induce or maintain remission by topical therapy at 600mg once followed by 300mg once every other week after the failure of topical corticosteroids prescribed by a specialized immunosuppressants physician. There have been two withdrawn drugs since February 2020 which are: alclomethasone and flumetasone.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in Eczema were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC).

Table 1. Addition of New SFDA Registered Drugs for the Management of Eczema

MAJOR CHANGES		
Addition of new molecules	**Drug class**	**HTA recommendations**
Baricitinib	Janus kinase (JAK) inhibitor	Negative recommendation from PBAC (2021)[6] because uncertainty in the clinical data and cost comparison presented in the submission did not capture the full cost and consequences of listing baricitinib. Positive recommendation for adult patients with moderate to severe atopic dermatitis who are eligible for systemic therapy in cases of ciclosporin failure, intolerance, or contraindication, and who have received the recommended dosages of MA from HAS (2021)[7]. Negative recommendation for ciclosporin-naive patients who have not adequately responded to topical treatments because of lack of comparative data in this specific patient group from HAS (2021)[7]. Positive recommendations from NICE (2021)[8], baricitinib is a cost-effective use of NHS resources and could be recommended as an option for people with moderate to severe atopic dermatitis when at least 1 systemic immunosuppressant has not worked or is not suitable. N/A for IQWIG and CADTH.
Upadacitinib	Janus Kinase (JAK) Inhibitor	From HAS (2021)[9]: Positive recommendation for the treatment of moderate to severe atopic dermatitis in adults who are candidates for systemic therapy in the event of failure, intolerance, or contraindication to ciclosporin and positive recommendation for the treatment of moderate to severe atopic dermatitis in adolescents 12 years

		and older who are candidates for systemic therapy. Negative recommendation for the treatment of moderate to severe atopic dermatitis in adults in whom topical therapies have failed and who are ciclosporin-naïve, in the absence of comparative data. Positive recommendation from PBAC (2021)[10]. From CADTH (2022)[11], the cost-effectiveness could not be estimated because of a lack of clinical data and limitations with the sponsor's model. N/A for NICE and IQWIG.
Tralokinumab	Monoclonal antibody (mAB)	From HAS (2021)[12], positive recommendation for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy in the event of failure, intolerance, or contraindication to ciclosporin. Negative recommendation when there is failure of topical treatments in ciclosporin-naive patients, in the absence of comparative data. From IQWIG (2023)[13], no added clinical benefit. From CADTH (2022)[14] negative recommendation, CADTH (2023) under process[15] N/A for NICE and PBAC.

Table 2. Addition of Non SFDA Registered Drugs for the Management of Eczema

MAJOR CHANGES	
Addition of new molecules	**Drug class**
Delgocitinib	Janus kinase (JAK) inhibitor
Abrocitinib	Janus kinase (JAK) inhibitor
Ruxolitinib **cream**	Janus kinase (JAK) inhibitor

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the management of eczema.

Below is a table summarizing the major changes based on the different eczema guidelines used to issue this report:

Table 3. General Recommendations for the Management of Eczema

Management of Eczema	
General Recommendations	**Level of Evidence/Grade of Recommendation and reference**
Topical corticosteroids (CS) appear to be effective for AD, thus they are recommended if used appropriately and potential side effects are considered.	Recommendation grade 1, Evidence level A[16]
The use of topical antimicrobial drugs for reducing the skin symptoms of AD is not recommended.	Evidence level A[16]
Topical tacrolimus is recommended for patients with AD aged ≥ 2years.	Recommendation grade 1, Evidence level A[16]
Delgocitinib ointment is recommended for patients with AD aged ≥ 2years.	Recommendation grade 1, Evidence level A[16]
The subcutaneous injection of dupilumab is recommended as remission induction and maintenance therapy for patients with moderate-to-severe AD in whom it is difficult to induce or maintain remission by topical therapy.	Recommendation grade 1, Evidence level A[16]
Baricitinib may be orally administered to patients with moderate to-severe AD in whom it is difficult to induce or maintain remission by topical therapy.	Recommendation grade 1, Evidence level A[16]
A topical anti-inflammatory treatment is recommended in the following circumstances for anal eczema: • In cases marked by highly inflammatory lesions to ensure rapid symptom relief. • Whenever treatment or elimination of causative factors as well as nonpharmacological measures have failed or are insufficiently effective.	N/A[17]

• Depending on the causative agent (trichophytes, epidermophytes, candida), antifungal agents with varying spectra of activity may be used.	
In cases of bacterial or fungal superinfection or pathogen-induced perianal dermatitis, appropriate topical and/or systemic treatments shall be initiated: <u>Bacterial superinfection</u>: • Preferential use of antiseptics • Topical bacteriostatic or bactericidal agents can be used alone or in combination with topical corticosteroids. • Depending on the clinical situation, use of systemic antibiotics must be considered. <u>Fungal superinfection</u>: • Topical antifungals can be used alone or, in case of severe inflammatory lesions, in combination with topical corticosteroids.	N/A[17]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Eczema clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: one part includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Eczema report, and another part includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the February 2020 CHI Eczema Report and the corresponding recommendations:

Table 4. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I and part II (2018)	N/A*
The American Academy of Dermatology guideline for care and management of atopic dermatitis with topical, systemic and phototherapy (2014)	The American Academy of Dermatology Guidelines of Care for the Management of Atopic Dermatitis in Adults with Topical Therapies (2023)[18]

*: No updated version available: the existing version is the most recent one and no further updates or revisions have been made or released.

1.1.1 The American Academy of Dermatology Guidelines of Care for the Management of Atopic Dermatitis in Adults with Topical Therapies (2023)

This guideline is an update on the AAD's 2014 guidelines of care for the management of atopic dermatitis[18].

Table 5. Strengths of Recommendations

Strength of Recommendation	Definition
Strong recommendation for the use of an intervention	Benefits clearly outweigh risk and burdens; recommendation applies to most patients in most circumstances.
Strong recommendation against the use of an intervention	Risk and burden clearly outweigh benefits; recommendation applies to most patients in most circumstances.
Good practice statement	Guidance was viewed by the Work Group as imperative to clinical practice and developed when the supporting evidence was considerable but indirect, and the certainty surrounding an intervention's impact was high with the benefits clearly outweighing the harms (or vice versa). Good practice statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high. Implementation of these strong recommendations is considered to clearly result in beneficial outcomes.
Conditional recommendation for the use of an intervention	Benefits are closely balanced with risks and burden; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values.
Conditional recommendation against the use of an intervention	Risks and burden closely balanced with benefits; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values.

Table 6. Certainty of Evidence

Certainty of Evidence	Definition
High	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	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	Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low	The estimate of effect is very uncertain; the true effect may be substantially different from the estimate of effect.

Nonprescription therapies:

- For adults with AD, the use of moisturizers is recommended. (Strong, moderate certainty of evidence)
- For adults with AD, bathing for treatment and maintenance is conditionally recommended. (Conditional, low certainty of evidence)
- For adults with moderate-to-severe AD experiencing a flare, the use of wet dressings is conditionally recommended. (Conditional, low certainty of evidence)

Topical calcineurin inhibitors:

- For adults with AD, the use of tacrolimus 0.03% or 0.1% ointment is recommended. (Strong, high certainty of evidence)
- For adults with mild-to-moderate AD, the use of pimecrolimus 1% cream is recommended. (Strong, high certainty of evidence)

Topical corticosteroids:

- For adults with AD, topical corticosteroids are recommended. (Strong, high certainty of evidence)
- For adults with AD, intermittent use of medium potency topical corticosteroids as maintenance therapy (2 times/wk) to reduce disease flares and relapse is recommended. (Strong, high certainty of evidence)

Topical antimicrobials/antiseptics and antihistamines:

- The use of topical antimicrobials for AD in adults is conditionally not recommended. (Conditional, low certainty of evidence)
- The use of topical antihistamines for AD in adults is conditionally not recommended. (Conditional, low certainty of evidence)
- The use of topical antiseptics for AD in adults is conditionally not recommended. (Conditional, very low certainty of evidence)

Topical PDE-4 inhibitors:

- For adults with mild-to-moderate AD the use of crisaborole ointment is recommended (Strong, high certainty of evidence)

Topical JAK inhibitors:

- For adults with mild-to-moderate AD, the use of ruxolitinib cream is recommended. (Strong, moderate certainty of evidence)

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI Eczema report, along with their recommendations.

Table 7. List of Additional Guidelines

Additional Guidelines
Japanese Dermatological Association English Version of Clinical Practice Guidelines for the Management of Atopic Dermatitis 2021[16]
Japanese Society of Allergology Guidelines for Atopic Dermatitis 2020[19]
European Academy of Dermatology and Venereology: European Task Force on Atopic Dermatitis Position Paper: Treatment of Parental Atopic Dermatitis During Preconception, Pregnancy, and Lactation Period 2019[20]
German Society of Dermatology S1 Guidelines for the Diagnosis and Treatment of Perianal Dermatitis (Anal Eczema) 2020[17]
Management of Atopic Dermatitis in Adults in Saudi Arabia: Consensus Recommendations from the Dermatological Expert Group 2022[21]
Consensus on the therapeutic management of atopic dermatitis – Brazilian Society of Dermatology 2019[22]
Diagnosis and Management of Moderate to Severe Adult Atopic Dermatitis: A Consensus by the Italian Society of Dermatology and Venereology (SIDeMaST), the Italian Association of Hospital Dermatologists (ADOI), the Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC), and the Italian Society of Allergological, Environmental and Occupational Dermatology (SIDAPA) 2018[23]
European Guideline (EuroGuiDerm) on Atopic Eczema: Part I – Systemic Therapy (2022)[24]
European Guideline (EuroGuiDerm) on Atopic Eczema: Part II – Non-Systemic Treatments and Treatment Recommendations for Special AE Patient Populations (2022)[25]

1.2.1 Japanese Dermatological Association Clinical Practice Guidelines for the Management of Atopic Dermatitis (2021)

The Japanese Dermatological Association published in 2021 its clinical practice guidelines for the management of AD. The main recommendations are summarized below[16]. Tables 6, 7, 8, and 9 describe the grading scheme used.

Table 8. Evidence Level

Level	Definition
High	The results are nearly established and unlikely to be markedly affected by future studies.
Low	There are studies that support the results, but the results are insufficient and may be markedly affected by future studies.
Very low	There are no high-quality studies that support the results.

Table 9. Designs of Studies Used as References for the Determination of the Evidence Level

Level	Definition
A	Many randomized controlled trials with high-quality and consistent results Meta-analyses of randomized controlled trials
B	Randomized controlled trials with inconsistent results. Randomized controlled trials of questionable quality or the presence of a few randomized controlled trials. Nonrandomized controlled trials Many controlled before-and-after trials or observational studies with consistent results.
C	A few controlled before-and-after trials or observational studies, case reports, and expert opinions.

Table 10. Recommendation Grade

Grade	Definition
1 Strong	The benefits obtained by the recommended treatment are judged to be large and surpass the harm or burdens caused by the treatment.

2 Weak	The magnitude of the benefits obtained by the recommended treatment is uncertain, or the benefits and harm or burdens that may result from the treatment are considered nearly equal.

Table 11. Clinical Significance of the Recommendation Grade and Evidence Level

Grade	Definition
1A	The evidence level is high, and the benefits obtained by the treatment are large and considered to surpass the harm or burdens that may be caused by the treatment. Therefore, the physician is advised to perform the recommended treatment.
1B/1C	Although the evidence level is low (B) or very low (C), the benefits obtained by the treatment are large and considered to surpass the harm and burdens that may be caused by the treatment. Therefore, the physician is advised to perform the recommended treatment with the understanding that the evidence is insufficient.
2A/2B/2C	The magnitude of the benefits obtained by the recommended treatment is uncertain, or the benefits are nearly equal to the harm or burdens caused by the treatment. The evidence level is high (A), low (B), or very low (C). Therefore, the physician is advised to select and propose the treatment and to confer with the patient about whether the treatment should be performed.

- TCS appear to be effective for AD, thus they are recommended if used appropriately and potential side effects are considered. (Recommendation grade 1, Evidence level A)
- It is desirable to reduce the application frequency of TCS and shift to a moisturizer after the disappearance of eruption in patients with moderate-to-severe AD who may experience relapses. (Evidence level C)
- The use of topical antimicrobial drugs for reducing the skin symptoms of AD is not recommended. (Evidence level A)
- Topical tacrolimus is recommended for patients with AD aged ≥ 2years. (Recommendation grade 1, Evidence level A)
- Delgocitinib ointment is recommended for patients with AD aged ≥ 2years. (Recommendation grade 1, Evidence level A)
- Antihistamines may reduce itching symptoms when used in combination with anti-inflammatory topical drugs and topical moisturizing drugs, therefore their use is proposed as an “add-on” therapy to topical anti-inflammatory treatment for AD. Non sedative second-generation

antihistamines should be selected. (Recommendation grade 2, Evidence level B)

- Proactive therapy is an effective treatment to maintain remission of eczema lesions and is a relatively safe treatment. Recommendation grade 1, Evidence level A.
- The use of topical moisturizing agents is recommended for dermatitis in combination with TCS or topical tacrolimus. The continuous use of a topical moisturizer is recommended even after reducing symptoms of dermatitis during the acute phase. (Recommendation grade 1, Evidence level A)
- Currently, the application of moisturizers in neonates for the prevention of AD onset is not unconditionally recommended. (Recommendation grade 2, Evidence level B)
- For patients with AD in whom control is difficult, despite the application of TCS or tacrolimus, skin care, and elimination of triggering factors, cyclosporin therapy may be selected. (Recommendation grade 2, Evidence level A)
- Phototherapy may be performed in patients in whom the relief of AD is not achieved by topical therapy, skin care, or strategies to avoid exacerbating factors or in patients with moderate-to-severe AD with adverse reactions to conventional treatment. (Recommendation grade 2, Evidence level B)
- The subcutaneous injection of dupilumab is recommended as remission induction and maintenance therapy for patients with moderate-to-severe AD in whom it is difficult to induce or maintain remission by topical therapy. (Recommendation grade 1, Evidence level A)
- Baricitinib may be orally administered to patients with moderate to-severe AD in whom it is difficult to induce or maintain remission by topical therapy. (Recommendation grade 1, Evidence level A)
- Currently, neither probiotics/prebiotics nor synbiotics in which both are combined are recommended to reduce AD symptoms. (Evidence level B)
- The administration of probiotics or prebiotics for the prevention of AD onset is not recommended. (Evidence level B)
- Many epidemiological observational studies and meta-analyses have suggested that the administration of antihistamines during pregnancy does not increase the incidence of congenital anomalies, but the evidence is insufficient. If the therapeutic advantage of administration is great, drugs that are reported to be safe may be administered after receiving informed consent by explaining the risk in comparison with the incidence of malformations as a background (2–3%). Although very small amounts of drug are transferred to

breastmilk, package inserts of most drugs state avoidance of breastfeeding; caution is thus needed. Regarding individual drugs, careful consideration of the contents of package inserts and the latest information on safety profiles is also necessary. (Evidence level B)

- The use of TCS according to standard methods during pregnancy or lactation is safe. They may be used without worrying about their influence on fetuses or infants. However, the use of high dose potent topical steroids for extended periods should be avoided because these may cause low weight at birth. (Evidence level B)
- Soap and detergents may be useful for the management of AD if specific skin conditions, type of soap and detergent, and cleaning methods are considered. (Recommendation grade 1, Evidence level C)
- No medical evidence actively recommends the use of povidone iodine solution. It may be considered an adjuvant therapy for cases that are difficult to treat using first line TCS because of infection, but povidone-iodine should not be used without careful consideration of safety concerns. (Evidence level C)
- This figure is adapted from the Clinical Practice Guidelines for the Management of Atopic Dermatitis 2021 and represents a summary algorithm for the treatment of atopic dermatitis.

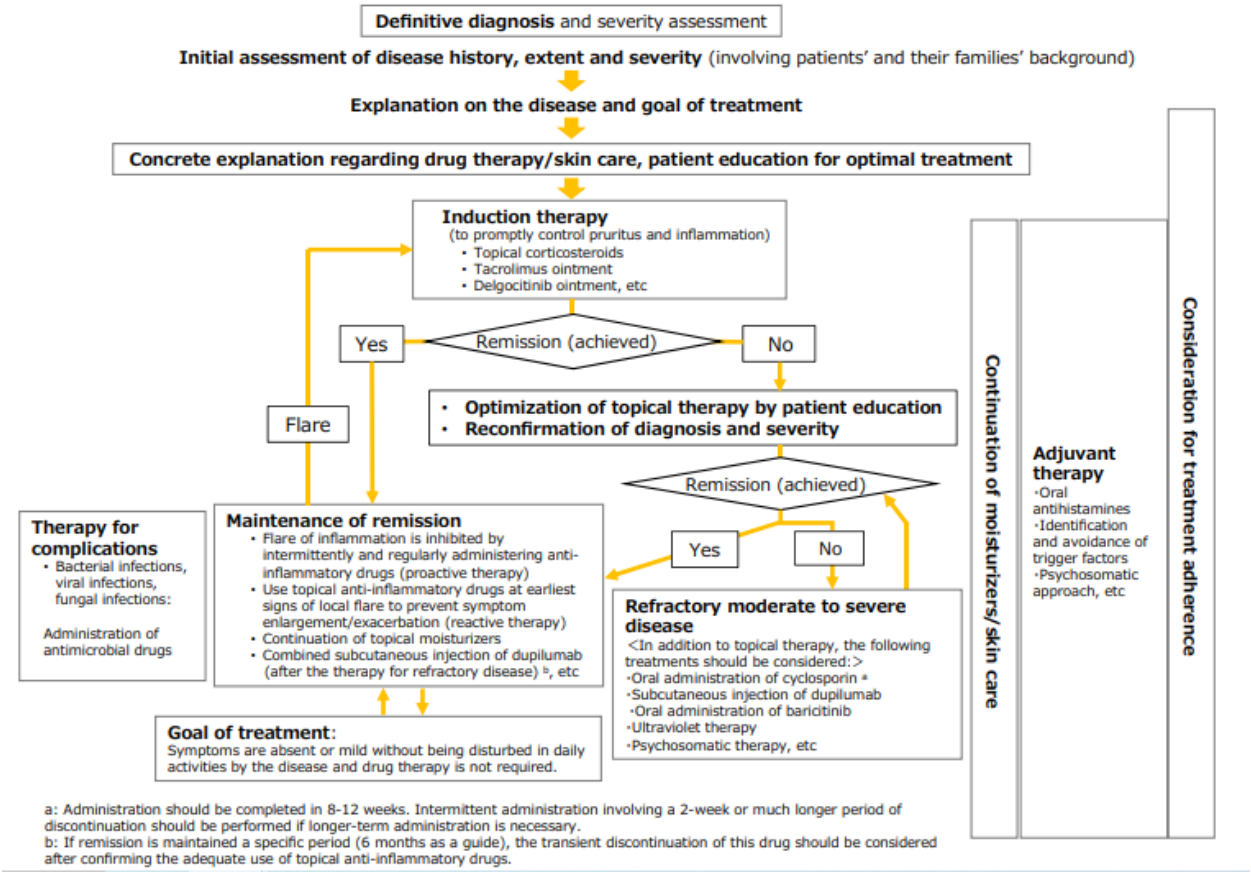

Figure 1. *Algorithm for the Treatment of Atopic Dermatitis. Adapted from Saeki H, Ohya Y, Furuta J, et al. English Version of Clinical Practice Guidelines for the Management of Atopic Dermatitis 2021. Journal of Dermatology. 2022;49(10):e315-e375. doi:10.1111/1346-8138.16527*

1.2.2 Japanese Society of Allergology Guidelines for Atopic Dermatitis (2020)

The main recommendations of the Japanese guidelines for atopic dermatitis are listed below[19]:

- TCS is often used as a first-line anti-inflammatory topical agent for both children and adults.
- Selection of rank. In Japan, TCS are generally classified into 5 ranks: strongest (Group 1), very strong (Group 2), strong (Group 3), medium (Group 4), and weak (Group 5) (Table 3). It is important to adequately select drugs at a rank that matches the severity of each eruption and use them at the required volume for the required period.

Table 12. Severity of Eruption and Topical Corticosteroid (TCS) Application

Severity	Eruption	TCS Application
Severe	Primarily severe swelling/ edema/infiltration or erythema with lichenification, multiple papules, severe scales, crusts, vesicles, erosion, multiple excoriations and pruriginous nodules.	Use of very strong or strong rank TCS is the first-line treatment. Strongest rank TCS are also available for refractory pruriginous nodules if sufficient effects are not achieved by applying very strong rank TCS
Moderate	Primarily moderate erythema, scales, a few papules, and excoriations.	Use of strong or medium rank TCS is the first-line treatment
Mild	Primarily dryness, mild erythema, and scales.	Use of medium or weak rank TCS is the first-line treatment
Slight	Primarily dryness with negligible inflammation.	Topical application of medicines other than TCS (emollients)

Table.13 Rank of Corticosteroids

Rank	Corticosteroid
Strongest	0.05% clobetasol propionate 0.05% diflorasone diacetate
Very Strong	0.1% mometasone furoate 0.05% betamethasone butyrate propionate 0.05% fluocinonide 0.064% betamethasone dipropionate 0.05% difluprednate 0.1% amcinonide 0.1% diflucortolone valerate 0.1% hydrocortisone butyrate propionate
Strong	0.3% deprodone propionate 0.1% dexamethasone propionate 0.12% dexamethasone valerate 0.1% halcinonide 0.12% betamethasone valerate 0.025% fluocinolone acetonide
Medium	0.3% prednisolone valerate acetate

	0.1% triamcinolone acetonide 0.1% alclometasone dipropionate 0.05 clobetasone butyrate 0.1% hydrocortisone butyrate 0.1% dexamethasone
Weak	0.5% prednisolone

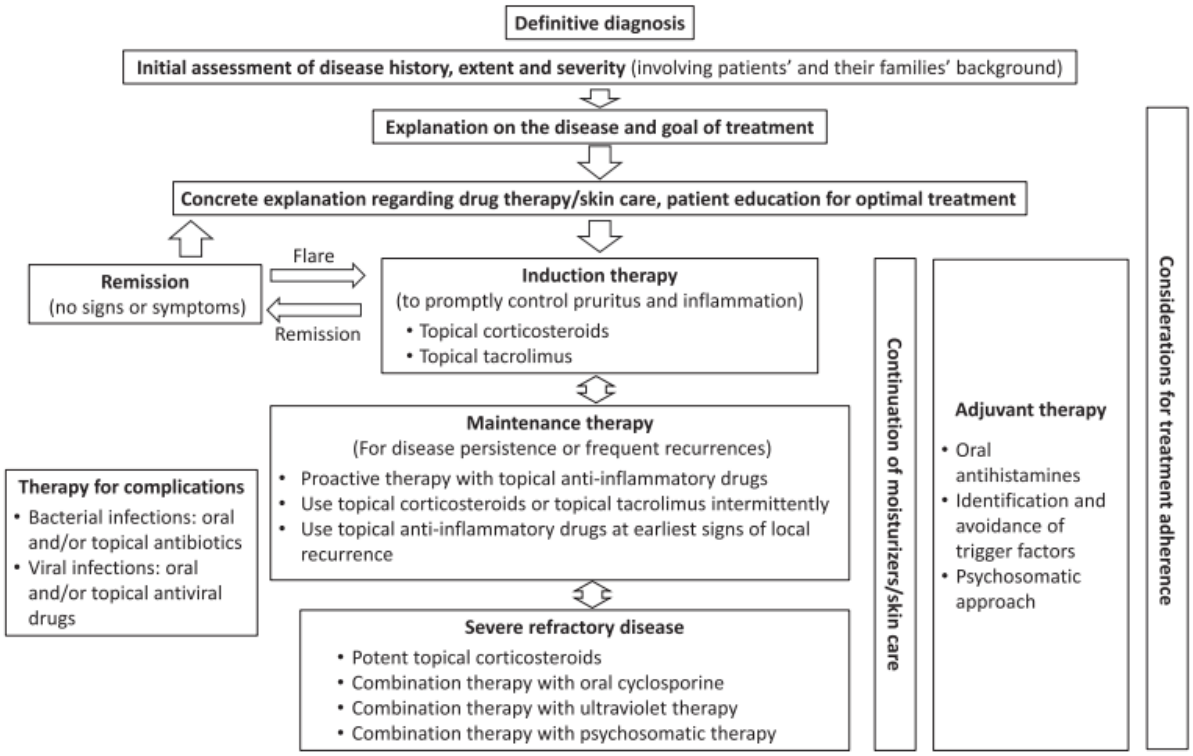

Figure 2. *Algorithm for the Management of Atopic Dermatitis. Adapted from Katoh N, Ohya Y, Ikeda M, et al. Japanese guidelines for atopic dermatitis 2020. Allergology International. 2020;69(3):356-369. doi:10.1016/j.alit.2020.02.006*

1.2.3 European Academy of Dermatology and Venereology: European Task Force on Atopic Dermatitis (ETFAD) Position Paper: Treatment of Parental Atopic Dermatitis During Preconception, Pregnancy, and Lactation Period (2019)

The recommendations for pregnancy specific population coming from the European task force on atopic dermatitis are listed in the tables below[20]:

Table 14. ETFAD Recommendations for Topical Corticosteroids

Topical Corticosteroids		
Women	Preconceptive	No restrictions
	Pregnant	TCS class II or III are recommended. If the use exceeds 200 g/month, additional UV treatment should be considered. Class IV may be used as rescue therapy, or over longer periods on limited skin areas. Fluticasone propionate should be avoided.
	Lactating	Should be applied immediately after breastfeeding, and nipples should be cleaned gently and carefully before feeding.
Men	Preconceptive	No restrictions

Table 15. ETFAD Recommendations for Topical Calcineurin Inhibitors

Topical Calcineurin Inhibitors		
Female	Preconceptive	No restrictions
	Pregnant	No restrictions
	Lactating	Should be applied immediately after breastfeeding, and nipples should be cleaned gently and carefully before feeding
Men	Preconceptive	No restrictions

Table 16. ETFAD Recommendations for Topical PDE-4 Inhibitors- Crisaborole

Topical PDE-4 Inhibitors		
Female	Preconceptive	Not recommended
	Pregnant	Not recommended
	Lactating	Not recommended
Men	Preconceptive	No restrictions

Table 17. ETFAD Recommendations for Cyclosporine A

Cyclosporine A		
Female	Preconceptive	May be used
	Pregnant	May be used under strict indications, is first-line therapy for long-term control

	Lactating	May be used under strict indications
Men	Preconceptive	No restrictions

Table 18. ETFAD Recommendations for Azathioprine

Azathioprine		
Female	Preconceptive	May be used
	Pregnant	May be used under strict indications if no other therapy is possible. It is not recommended to initiate therapy during pregnancy where other therapies should be used
	Lactating	May be used, but it is recommended to discard milk produced within 4 hours after drug intake.
Men	Preconceptive	No restrictions

Table 19. ETFAD Recommendations for Methotrexate

Methotrexate		
Female	Preconceptive	Therapy must be stopped 6 months prior to desired time of conception if no local/national guidelines exist. Local/National guidelines supersedes this recommendation.
	Pregnant	Contraindicated
	Lactating	Contraindicated
Men	Preconceptive	Therapy must be stopped 3 months prior to desired time of conception

Table 20. ETFAD Recommendations for Mycophenolate Mofetil

Mycophenolate Mofetil		
Female	Preconceptive	Therapy must be stopped 3 months prior to desired time of conception
	Pregnant	Contraindicated
	Lactating	Contraindicated
Men	Preconceptive	Therapy must be stopped 3 months prior to desired time of conception

Table 21. ETFAD Recommendations for Systemic Corticosteroids

Systemic Corticosteroids		
Female	Preconceptive	May be used as rescue therapy, or as bridging until effect of other systemic or biological medicaments
	Pregnant	May be used as rescue therapy, or for short periods of time (2–3 weeks), not exceeding 0.5 mg/kg/day. Prednisolone is the preferred drug
	Lactating	May be used as rescue therapy
Men	Preconceptive	No restrictions compared to the ETFAD position paper on atopic dermatitis

1.2.4 German Society of Dermatology S1 Guidelines for the Diagnosis and Treatment of Perianal Dermatitis (Anal Eczema) (2020)

The recommendations of the German Society of Dermatology clinical guidelines for the diagnosis and treatment of perianal dermatitis are listed below[17]:

Non-pharmacological treatment:

- Optimized anal hygiene
- Detergent-free cleansing with tepid water (anal douching or sitz baths)
- Gentle drying with cotton pads, soft towels, or unbleached, fragrance-free paper towels.
- Optimized bowel movement habits
- Dietary modifications aimed at achieving formed stool.
    - If applicable: reduction in the frequency of bowel movements
    - If applicable: supplemental intake of bulking agents (e.g., psyllium)
- Skin care and protection
- Gentle, allergen-free skin care products (e.g., hydrophilic oil-in-water preparations)
- Skin protection with zinc oxide paste
- Use of loose cotton underwear (to avoid constriction)

Pharmacological treatment:

A **topical anti-inflammatory** treatment is recommended in the following circumstances:

- In cases marked by highly inflammatory lesions to ensure rapid symptom relief.
- Whenever treatment or elimination of causative factors as well as nonpharmacological measures have failed or are insufficiently effective.
- In cases of bacterial or fungal superinfection or pathogen-induced perianal dermatitis, appropriate topical and/or systemic treatments shall be initiated:
    - Bacterial superinfection:
        - Preferential use of antiseptics
        - Topical bacteriostatic or bactericidal agents can be used alone or in combination with topical corticosteroids.
        - Depending on the clinical situation, use of systemic antibiotics must be considered
    - Fungal superinfection:
        - Topical antifungals can be used alone or, in case of severe inflammatory lesions, in combination with topical corticosteroids.
        - Depending on the causative agent (trichophytes, epidermophytes, candida), antifungal agents with varying spectra of activity may be used.

1.2.5 Management of Atopic Dermatitis in Adults in Saudi Arabia: Consensus Recommendations from the Dermatological Expert Group

The recommendations of the management of Atopic Dermatitis in Adults in Saudi Arabia: Consensus Recommendations from the Dermatological Expert Group published in 2022 are listed below[21]:

- In AD patients who are not adequately controlled with topical therapy or systemic therapies, the preferred systemic agent for use either alone or in combination with topical treatments is dupilumab, cyclosporine, methotrexate, phototherapy, or other available systemic treatments. (100% agreement).
- Moisturizers are the front-line, basic, nonpharmacologic treatment strategies for the management of both acute and proactive AD and their application is usually recommended after bathing.

- When nonpharmacologic interventions fail, TCS is recommended as the front-line therapy and should be used with caution in patients with thin skin.
- TCIs are alternatives to patients showing an increased risk of adverse events with TCS. They are specifically beneficial in sensitive areas, such as the skin folds and face.
- Topical antimicrobial bleach baths, that is, 0.005% sodium hypochlorite, are recommended two times a week in patients at a greater risk of skin infections.
- Phototherapy is recommended for unmanageable AD or for patients who are refractory to topical regimens. The use of narrow-band ultraviolet B is preferred.
- Systemic immunosuppressants are recommended in severe AD patients who were unmanageable with topical regimens and phototherapy.
- Systemic corticosteroids are not advised for the management of chronic AD. However, atopic flares may develop with a short course of these agents after discontinuation.
- In patients with confirmed infection, systemic antibiotics are recommended, and systemic antivirals are recommended in patients with eczema herpeticum.

1.2.6 Consensus on the Therapeutic Management of Atopic Dermatitis – Brazilian Society of Dermatology 2019

The recommendations of the Brazilian society of dermatology on the therapeutic management of atopic dermatitis are listed below[22]:

- Topical anti-inflammatory therapy is the mainstay of AD treatment. Anti-inflammatory agents must have sufficient potency and should be applied on the skin lesions according to the recommendations and not exceeding the allowed amount per day.
- TCS are the first line treatment for AD, with strong evidence of their superiority over placebo. TCS use depends on the vehicle; as a cream, they should be applied 15 minutes before the moisturizer, and as an ointment, applied 15 minutes prior to the moisturizer.
- Tacrolimus and pimecrolimus are second-line non-corticosteroid, anti-inflammatory therapies for AD with proven efficacy.
- Proactive treatment has been proposed in published guidelines. It consists of long-term use of topical anti-inflammatory agents, either TCS or TIM

(tacrolimus), twice a week in previously affected areas, combined with moisturizers.

- The use of topical antibiotics and antiseptics is still variable. Topical antibiotics can be used for short periods, and bleach (0.005% sodium hypochlorite may be useful for pediatric AD). Wet-wrap bandages or occlusive treatment during hospitalization are helpful measures for improving flares.
- Systemic treatment of AD is recommended in moderate to severe cases that fail to respond to topical therapies. Before initiating systemic treatment, it is mandatory to avoid aggravating factors, to diagnose and treat secondary infections, and to rule out differential diagnoses.
- Cyclosporin Ais approved in many European countries and in Brazil for severe AD. The U.S. FDA approves it for psoriasis. The initial dose for children and adults varies from 3 to 5 mg/kg/day, and the maintenance dose is from 2.5 to 3 mg/kg/day.
- MTX can be indicated as initial treatment for moderate/severe AD, recalcitrant to topical treatment with corticosteroids.
- AZA can be indicated as systemic treatment for refractory AD.
- Clinical efficacy of Mycophenolate mofetil is reached after 8-12 weeks of use (off label in AD), and the drug has a good safety profile.
- Oral corticosteroids are used in exceptional cases for short periods (up to 1 week).
- Oral antibiotics are indicated when there are signs of bacterial superinfection of the skin; cephalosporins are the first choice, followed by sulfamethoxazole-trimethoprim.
- Eczema herpeticum must be treated with systemic antiviral drugs; when it is followed by systemic symptoms and signs, hospitalization and intravenous antiviral therapy are indicated.
- AD patients with head and neck involvement may benefit from treatment with antifungal agents.

1.2.7 Diagnosis and management of moderate to severe adult atopic dermatitis: a Consensus by the Italian Society of Dermatology and Venereology (SIDeMaST), the Italian Association of Hospital Dermatologists (ADOI), the Italian Society of Allergy, Asthma and Clinical Immunology (SIAAIC), and the Italian Society of Allergological, Environmental and Occupational Dermatology (SIDAPA) 2018

The recommendations of the Italian guideline on diagnosis and management of moderate to severe atopic dermatitis are listed below[23]:

- A patient with AD is considered non-responder to traditional systemic therapies – cyclosporine (on label in Italy), methotrexate, and azathioprine (off label in Italy) – or phototherapy – UVB-NB, UVA 1, and PUVA (where available) – when he/she has not achieved an improvement of the considered severity indices of at least 50%.
- In case of recurrence within 1 month from therapy discontinuation, with a clinically significant increase of severity indices, a different therapeutic option should be considered.
- In case of recurrence within 3 months from therapy discontinuation, with a clinically significant increase of severity indices, a different therapeutic option may be considered.
- Systemic corticosteroids should be considered only in case of acute flares and for a maximal duration of 1 month. A duration >1 month may be considered in non-responders to other systemic treatments.
- Patients with moderate-severe AD, who are non-responder or intolerant, have contraindications or are anyway non-eligible to CyA or phototherapy, are eligible to biological therapy.

1.2.8 European Guideline (EuroGuiDerm) on Atopic Eczema: Part I – Systemic Therapy (2022)

The European guidelines on atopic eczema for systemic therapy issued the following recommendations: [24]

Table 22. Interpretation of Recommendation Strengths

Strength	Implications
Strong recommendation **for** the use of an intervention	We believe that all or almost all informed people would make this choice.
Weak recommendation **for** the use of an intervention	We believe that most informed people would make this choice, but a substantial number would not
No recommendation with respect to an intervention	Now, a recommendation in favor of or against an intervention cannot be made due to certain reasons (e.g., no reliable evidence available, conflicting outcomes)
Weak recommendation **against** the use of an intervention	We believe that most informed people would make a choice against this intervention, but a substantial number would not.
Strong recommendation **against** the use of an intervention	We believe that all or almost all informed people would make a choice against this intervention.

- The use of Azathioprine in AE patients who are candidates for systemic treatment is suggested. (Weak recommendation)
- The use of ciclosporin to achieve disease control in AE patients who are candidates for systemic treatment is recommended. (Strong recommendation)
- Start with higher ciclosporin dosages to achieve a more rapid response in AE patients who are candidates for systemic treatment is recommended. (Strong recommendation)
- Close follow-up for potential blood pressure elevation and signs of renal impairment in AE patients on ciclosporin is recommended. (Strong recommendation)
- Systemic glucocorticosteroids only as rescue therapy for acute flares in AE patients is suggested. (Weak recommendation)
- The long-term use of systemic glucocorticosteroids in AE patients is not recommended. (Strong recommendation against)

- Methotrexate in AE patients who are candidates for systemic treatment is suggested. (Weak recommendation)
- Dupilumab in AE patients who are candidates for systemic treatment is recommended. (Strong recommendation)
- No recommendations can be made concerning mycophenolate and omalizumab for the treatment of AE.
- Tralokinumab in AE patients who are candidates for systemic treatment is recommended. (Strong recommendation)
- Baricitinib in AE patients, who are candidates for systemic treatment is recommended. (Strong recommendation)
- Upadacitinib in AE patients who are candidates for systemic treatment is recommended. (Strong recommendation)
- Alitretinoin for AE patients with severe chronic hand eczema, who are candidates for systemic treatment, duely considering its teratogenicity is suggested. (Weak recommendation)

1.2.9 European Guideline (EuroGuiDerm) on Atopic Eczema: Part II – Non-Systemic Treatments and Treatment Recommendations for Special AE Patient Populations

The European guidelines on atopic eczema for non-systemic treatment for special atopic eczema patient populations listed the below recommendations[25]:

Basic emollients and moisturizers:

- Gentle cleansing and bathing procedures, especially in acutely inflamed or superinfected skin in patients with AE are recommended. (Strong recommendation)
- Bathing in moderately warm water over a short duration of time in patients with AE is suggested. (Weak recommendation)
- Daily use of emollients, liberally and frequently for patients with AE, as basic treatment of the disturbed skin barrier function is recommended. (Strong recommendation)
- Moisturizers with a hydrophilic formula in the summer and moisturizers with a higher lipid content in the winter in patients with AE are suggested. (Weak recommendation)
- The use of emollients as background treatment to prevent flares and to reduce the symptoms of AE is recommended. (Strong recommendation)

- **Anti-inflammatory treatment:**
- The use of topical corticosteroids (TCS) as anti-inflammatory agents is recommended. (Strong recommendation)
- The use of topical calcineurin inhibitors (TCI) as anti-inflammatory agents is recommended. (Strong recommendation)
- TCS in AE especially for treatment of acute flares is recommended. (Strong recommendation)
- The use of TCI particularly in skin areas with a risk of skin atrophy due to TCS application (face, intertriginous sites, anogenital area) is recommended. (Strong Recommendation)
- Proactive therapy (e.g., twice weekly application) with a suitable TCS or a suitable TCI to reduce the risk of relapse and for better disease control is recommended. (Strong Recommendation)

Anti-microbial treatment:

- Treatment with topical antiseptic drugs – including sodium hypochlorite 0.005% baths - in patients with a history of recurrent skin infections is suggested. (Weak recommendation)
- Topical anti-inflammatory treatments are continued during the treatment of Staphylococcus aureus superinfection episodes are suggested. (Weak recommendation)
- Treat eczema herpeticum without delay using systemic antiviral therapy, such as acyclovir is recommended. (Strong recommendation)
- Topical or systemic antifungal therapy in some patients with AE, mainly in those suffering from the “head and neck” variant of AE and with demonstrated IgE-sensitization to Malassezia spp. Is suggested. (Weak recommendation)

Topical antihistamines:

- Topical antihistamines in itch treatment in AE is not recommended. (Strong recommendation against)

Systemic antihistamines:

- Using first- and second-generation systemic antihistamines as a long-term treatment for itch in AE is not recommended. (Strong recommendation against)

Section 2.0 Drug Therapy

This section comprises four subsections: the first contains the newly recommended drugs that are SFDA registered, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details the new drugs that are not SFDA registered but FDA/EMA approved.

2.1 Additions

After February 2020, there have been two new drugs that have received FDA and EMA approval and one new drug that received EMA approval are SFDA registered. This section will include all characteristics describing Baracitinib, Upadacitinib and Tralokinumab as well as their HTA analysis respectively.

2.1.1 Baricitinib

The following table describes the characteristics of drug Baricitinib[26,27]:

Table 23. Drug Therapy with Baricitinib

SCIENTIFIC NAME BARICITINIB	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	No
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L20
Drug Class	DISEASE MODIFYING
Drug Sub-class	JANUS KINASE INHIBITOR (JAK)
ATC Code	L04AA37
Pharmacological Class (ASHP)	JANUS KINASE INHIBITOR (JAK)
DRUG INFORMATION	
Dosage Form	Film coated tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	**4 mg once daily.** A dose of 2 mg once daily is recommended for patients at higher risk of VTE, MACE and malignancy, for patients aged ≥ 65 years and for

	patients with a history of chronic or recurrent infections. A dose of 4 mg once daily may be considered for patients who do not achieve adequate control of disease activity with 2 mg once daily dose. A dose of 2 mg once daily should be considered for patients who have achieved sustained control of disease activity with 4 mg once daily and are eligible for dose tapering.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	The safety and efficacy of baricitinib in children and adolescents aged 0 to 18 years have not yet been established. No data are available.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Renal impairment The recommended dose is 2 mg once daily in patients with creatinine clearance between 30 and 60 mL/min. Baricitinib is not recommended for use in patients with creatinine clearance < 30 mL/min. Hepatic impairment No dose adjustment is required in patients with mild or moderate hepatic impairment. Baricitinib is not recommended for use in patients with severe hepatic impairment.
Prescribing edits*	AGE, PA, MD, ST
AGE (Age Edit): Only approved for atopic dermatitis for patients 18 years and older because the safety and efficacy of baricitinib was not established in children and adolescents 0 to 18 years.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Baricitinib is an immunomodulatory and needs a specialist physician for prescription	
PA (Prior Authorization): This drug should be given to patients with moderate to-severe AD in whom it is difficult to induce or maintain remission by topical	

therapy. The recommended dose of baricitinib is 4mg orally once daily, with or without topical corticosteroids.	
QL (Quantity Limit): N/A	
ST (Step Therapy): This drug is used if remission was not maintained by topical therapy, therefore is comes as a second line treatment.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common**: increased LDL cholesterol, upper respiratory tract infections, headache, herpes simplex and urinary tract infections.
Drug Interactions*	**Category X**: • Abrocitinib • Anifrolumab • BCG intravesical • BCG Products • Brivudine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Fexinidazole • Filgotinib • Immunosuppressants (Cytotoxic chemotherapy) • Immunosuppressants (miscellaneous oncologic agents) • Immunosuppressants (therapeutic immunosuppressant agents) • InFLIXimab • Mumps- Rubella- or Varicella Containing Live Vaccines • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Trivalent/Oral) • Ritlecitinib • Ruxolitinib (Topical) • Tacrolimus (Topical) • Talimogene Laherparepvec

	• Taurursodiol • Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Vaccines (Live) • Yellow Fever Vaccine
Special Population	Clinical experience in patients aged ≥ 75 years is very limited.
Pregnancy	Baricitinib is contraindicated during pregnancy. Women of childbearing potential must use effective contraception during and for at least 1 week after treatment. If a patient becomes pregnant while taking baricitinib the parents should be informed of the potential risk to the fetus.
Lactation	A risk to newborns/infants cannot be excluded and baricitinib should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue therapy considering the benefit of breast-feeding for the child and the benefit of therapy for the woman. Available pharmacodynamic/toxicological data in animals have shown excretion of baricitinib in milk.
Contraindications	Hypersensitivity to the active substance or to any of the excipients. List of excipients: iron oxide red (E172) lecithin (soya) (E322), macrogol, poly (vinyl alcohol), talc, titanium dioxide (E171).
Monitoring Requirements	In all patients: Lymphocyte, neutrophil, platelet counts, and Hb, LFTs, and renal function (baseline and periodically thereafter); signs/symptoms of

	infections (including tuberculosis) during and after therapy.
Precautions	Baricitinib should only be used if no suitable treatment alternatives are available in patients: • 65 years of age and older • Patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers) • Patients with malignancy risk factors (e.g., current malignancy or history of malignancy)
Black Box Warning	• Serious infections • Mortality • Malignancies • Major adverse cardiovascular events (MACE) • Thrombosis
REMS*	N/A

Health Technology Assessment (HTA)

The below table lists the health technology Assessment recommendations for Baracitinib by the National Institute for Health and Care Excellence (NICE), the Haute Autorite de Sante (HAS) and the Pharmaceutical Benefits Advisory Committee (PBAC).

Table 24. Baracitinib HTA Analysis

Medication	Agency	Date – HTA Recommendation
Baracitinib	PBAC[6]	July 2021: **Not recommended**- The PBAC declined to recommend the inclusion of baricitinib for the treatment of severe AD in adults. While acknowledging the reasonable claim of baricitinib's inferior efficacy compared to dupilumab, the PBAC found the magnitude of difference in response uncertain. Additionally, the PBAC recognized that baricitinib's safety profile was less favorable than dupilumab's, and concerns persisted regarding its long-

		term safety. As a result, the PBAC deemed the clinical position of baricitinib unclear. Moreover, due to the uncertainty surrounding the clinical data and the incomplete cost assessment presented in the submission, the PBAC considered the economic analysis unreliable for deciding on listing baricitinib.
	HAS[7]	<u>February 2021:</u> The Committee provides a **positive recommendation** for adding the medicinal product to both the hospital and retail formulary lists for reimbursed proprietary medicines. This approval applies to its use in adult patients with moderate to severe atopic dermatitis who are eligible for systemic therapy in cases of ciclosporin failure, intolerance, or contraindication, and who have received the recommended market authorization dosages. The Committee issues a **negative recommendation** for including the medicinal product in both the hospital and retail formulary lists for reimbursed proprietary medicines concerning ciclosporin-naive patients who have not adequately responded to topical treatments. This decision is due to the absence of comparative data in this specific patient group. ≈ Recommended reimbursement rate: 15%
	NICE[8]	<u>March 2021:</u> The pairwise ICERs suggested that baricitinib was **cost effective** compared with both dupilumab and best supportive care. Incremental analyses supported the cost effectiveness of baricitinib when used before or after dupilumab, despite uncertainty. Also, the summary of product characteristics states that response to baricitinib may be assessed from 8 weeks rather than the 16 weeks used in the model. This would likely improve the cost effectiveness of baricitinib. The committee concluded that baricitinib is a cost-effective use of NHS resources and could be recommended as an option for people with moderate to severe atopic dermatitis when at least 1 systemic immunosuppressant has not worked or is not suitable. Given the QALY losses

		for baricitinib compared with dupilumab, treatment choice should be a decision made between the doctor and the patient.
	IQWIG	N/A
	CADTH	N/A

Conclusion Statement – Baricitinib

Baricitinib may be orally administered to adults with moderate to-severe AD in whom it is difficult to induce or maintain remission by topical therapy at a dose of 4 mg once daily. As for the HTA analysis, PBAC does not recommend Baricitinib because the economic analysis was unreliable. HAS issued a positive recommendation for adult patients with moderate to severe atopic dermatitis who are eligible for systemic therapy in cases of ciclosporin failure, intolerance, or contraindication, and who have received the recommended dosages. Moreover, HAS issued a negative recommendation for ciclosporin-naive patients who have not adequately responded to topical treatments. NICE HTA conclusion was that baricitinib is a cost-effective use of NHS resources and could be recommended as an option for people with moderate to severe atopic dermatitis when at least 1 systemic immunosuppressant has not worked or is not suitable.

2.1.2 Upadacitinib

Upadacitinib (Rinvoq) was approved by the FDA in 2022[28], and by the EMA in 2021[29].

Upadacitinib is an oral JAK1 inhibitor approved by the FDA and EMA for adults and adolescents aged 12+ years with moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable[30]. It is supplied as a prolonged release tablet for oral administration. The recommended dosage is 15 mg once daily; may increase to 30 mg once daily if inadequate response[31].

The following table describes the characteristics of drug Upadacitinib[31–33]:

Table 25. Drug Therapy with Upadacitinib

SCIENTIFIC NAME UPADACITINIB	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes

PMDA	Yes
Indication (ICD-10)	L20
Drug Class	IMMUNOSUPRESSANT
Drug Sub-class	JANUS KINASE (JAK) INHIBITORS
ATC Code	L04AA
Pharmacological Class (ASHP)	Janus Kinase (Jak) Inhibitors
DRUG INFORMATION	
Dosage Form	Prolonged-release tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	Oral: 15 mg once daily; may increase to 30 mg once daily if inadequate response. Discontinue if an adequate response is not achieved with the 30 mg dose; use the lowest effective dose needed to maintain response.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Atopic dermatitis, refractory, moderate to severe: Children ≥12 years and Adolescents, weighing ≥40 kg: Oral: 15 mg once daily; may increase to 30 mg once daily if inadequate response
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Altered kidney function: - eGFR ≥30 mL/minute/1.73 m2: No dosage adjustment necessary. - eGFR 15 to <30 mL/minute/1.73 m2: 15 mg once daily. - eGFR <15 mL/minute/1.73 m2: Use is not recommended. Liver impairment: Mild to moderate impairment (Child-Pugh class A or B): No dosage adjustment is necessary. Severe impairment (Child-Pugh class C): Use is not recommended. Hematologic: Absolute lymphocyte count (ALC) <500/mm3: Interrupt therapy until ALC ≥500/mm3.

	ANC <1,000/mm3: Interrupt therapy until ANC ≥1,000/mm3. Hemoglobin <8 g/dL: Interrupt therapy until hemoglobin ≥8 g/dL. Hypersensitivity reaction (severe): Discontinue therapy. Infection (serious), including herpes zoster: Interrupt treatment until the infection is controlled.
Prescribing edits*	AGE, MD, PA, ST
AGE (Age Edit): only approved to treat adults and children 12 years of age and older with moderate to severe eczema.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in immunosuppressive therapy and management of dermatitis.	
PA (Prior Authorization): This drug should be given to treat adults and children 12 years of age and older with moderate to severe eczema (atopic dermatitis) at 15mg once daily after no response to previous treatment and eczema still not well controlled prescribed by physicians experienced in immunosuppressive therapy.	
QL (Quantity Limit): N/A	
ST (Step Therapy): treat moderate to severe eczema (atopic dermatitis) that did not respond to previous treatment and their eczema is not well controlled with other pills or injections, including biologic medicines, or the use of other pills or injections is not recommended.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common**: acne vulgaris, upper respiratory tract infection, folliculitis, skin rash. **Most serious**: hypersensitivity reaction, Infections, pneumonia, which may cause shortness of breath, fever, and a cough with mucus, sepsis, allergic reaction (chest tightness, wheezing, swelling of the lips, tongue or throat, hives)
Drug Interactions*	**Category X**: • Abrocitinib

	• Anifrolumab • Baricitinib • BCG intravesical • BCG Products • Brivudine • Cladribine • CYP3A4 inducers (strong) • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Dipyrone • Fexinidazole • Filgotinib • Fusidic acid • Grapefruit juice • Immunosuppressants (Cytotoxic Chemotherapy) • Immunosuppressants (Miscellaneous Oncologic Agents) • Immunosuppressants (Therapeutic Immunosuppressant Agents) • Mumps- Rubella- or Varicella Containing Live Vaccines • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Trivalent/Oral) • Ruxolitinib (Topical) • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Tofacitinib • Typhoid Vaccine • Upadacitinib • Vaccines (Live) • Yellow Fever Vaccine • Zavegepant
Special Population	Patients with rheumatic musculoskeletal disease undergoing hip or knee replacement surgery: Hold upadacitinib for at least 3 days prior to surgery to reduce infection risk; therapy

	can be restarted once surgical wound shows evidence of healing (egg, no swelling, erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk).
Pregnancy	Upadacitinib must not be used during pregnancy
Lactation	Do not use upadacitinib while breast-feeding as it is not known if this medicine passes into breast milk.
Contraindications	Hypersensitivity to upadacitinib or any component of the formulation.
Monitoring Requirements	Lymphocyte count, neutrophil count, hemoglobin, and LFTs (baseline and periodically thereafter); lipids (12 weeks after therapy initiation and periodically thereafter); viral hepatitis (prior to initiating therapy and periodically thereafter); latent and active tuberculosis (TB) screen at baseline; verify pregnancy status (prior to initiating therapy); signs/symptoms of infection (including TB) during and after therapy; skin examinations (periodically, in patients at increased risk for skin cancer); symptoms of thrombosis.
Precautions	-GI perforation → use with caution in patients at increased risk for GI perforation -Hematologic toxicity → do not initiate therapy in patients with an absolute lymphocyte count <500/mm3, ANC <1,000/mm3, or hemoglobin <8 g/dL. Monitor CBC at baseline and periodically thereafter. -Hepatic effects → monitor LFTs at baseline and periodically thereafter;

	interrupt therapy if LFTs increased and drug-induced liver injury is suspected. -Lipid abnormalities: Increased lipid parameters → assess lipids 12 weeks after upadacitinib initiation and manage lipid abnormalities according to current clinical guidelines. -Medication residue in stool → monitor patients for clinical response and consider alternative therapy if there is a lack of therapeutic response. -Tuberculosis → Use with caution in patients who have resided or traveled in regions where TB is endemic.
Black Box Warning	• Serious infections • Mortality • Malignancies • MACE • Thrombosis
REMS*	N/A

Health Technology Assessment (HTA)

The below table lists the health technology Assessment recommendations for Upadacitinib by the Haute Autorite de Sante (HAS) and the Pharmaceutical Benefits Advisory Committee (PBAC) and the Canadian Agency for Drugs and Technologies in Health (CADTH).

Table 26. Upadacitinib HTA Analysis

Medication	Agency	Date – HTA Recommendation
Upadacitinib	PBAC[10]	2021: **Positive recommendation** - The PBAC recommended the listing of upadacitinib for severe atopic dermatitis. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of upadacitinib would be acceptable if it were cost-minimised against dupilumab.
	HAS[9]	2021: *In adults*

		Favorable opinion for reimbursement in the treatment of moderate to severe atopic dermatitis in adults who are candidates for systemic therapy in the event of failure, intolerance, or contraindication to ciclosporin. **Unfavorable opinion** for reimbursement in the treatment of moderate to severe atopic dermatitis in adults in whom topical therapies have failed and who are ciclosporin-naïve, in the absence of comparative data. *In adolescents 12 years and older* Favorable opinion for reimbursement in the treatment of moderate to severe atopic dermatitis in adolescents 12 years and older who are candidates for systemic therapy.
	CADTH[11]	2022: The cost-effectiveness of the health Canada–recommended dosing strategy **could not be estimated** because of a lack of clinical data and limitations with the sponsor's model. As such, the cost-effectiveness of UPA is unknown.
	NICE	N/A
	IQWIG	N/A

Conclusion Statement - Upadacitinib

Rinvoq (upadacitinib) is an oral JAK-1 inhibitor approved by the FDA and EMA for adults and adolescents aged 12+ years with moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.[30] Upadacitinib is supplied as a prolonged release tablet for oral administration. The recommended dosage is 15 mg once daily; may increase to 30 mg once daily if inadequate response.[31] PBAC had a positive recommendation for the cost-effectiveness of upadacitinib. HAS had two different recommendations: positive for adults who are candidates for systemic therapy in the event of failure, intolerance, or contraindication to ciclosporin and adolescents 12 years and older who are candidates for systemic therapy. Negative for adults in whom topical therapies have failed and who are ciclosporin-naïve, in the absence of comparative data.

2.1.3 Tralokinumab

Tralokinumab was approved by the FDA for atopic dermatitis in December 2021[34], and by the EMA in June 2021[35].

Tralokinumab is a biologic drug approved by the FDA for adults (18+ years) with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies used on the skin (topical therapies) or when those therapies are not advisable[34]. It is supplied as a subcutaneous injection 600 mg (given as four 150 mg injections) once, followed by 300 mg (given as two 150 mg injections) once every other week[36].

The following table describes the characteristics of tralokinumab[36,37]:

Table 27. Drug Therapy with Tralokinumab

SCIENTIFIC NAME TRALOKINUMAB	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L20
Drug Class	MONOCLONAL ANTIBODY
Drug Sub-class	INTERLEUKIN-13 ANTAGONIST
ATC Code	D11AH07
Pharmacological Class (ASHP)	MONOCLONAL ANTIBODY (mAB)
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	SUBQ: 600 mg (given as four 150 mg injections) once, followed by 300 mg (given as two 150 mg injections) once every other week.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	There are no dosage adjustments provided in the manufacturer's labeling for kidney and liver impairment.
Prescribing edits*	AGE, MD, PA, ST

AGE (Age Edit): Only approved for adults and adolescent patients 12 years and older.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Only physicians experienced in immunosuppressive therapy.	
PA (Prior Authorization): This drug should be given to treat adults and adolescents 12 years of age and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy at 600 mg (given as four 150 mg injections) once, followed by 300 mg (given as two 150 mg injections) once every other week prescribed by physicians experienced in immunosuppressive therapy.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Tralokinumab is used when atopic dermatitis **is not adequately controlled with topical prescription therapies or when those therapies are not advisable**	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common**: upper respiratory tract infection, injection site reactions, conjunctivitis, and allergic conjunctivitis.
Drug Interactions*	**Category X**: • Vaccines (live)
Special Population	In patients with body weight <100 kg who achieve clear or almost clear skin after 16 weeks of therapy, may reduce dosage to 300 mg every 4 weeks.
Pregnancy	There is limited amount of data from the use of tralokinumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy.
Lactation	It is not known if tralokinumab is present in breast milk.
Contraindications	Hypersensitivity to tralokinumab or any component of the formulation.

Monitoring Requirements	Monitor for signs/symptoms of hypersensitivity reactions and ocular adverse effects.
Precautions	Hypersensitivity reactions → If signs/symptoms of a serious hypersensitivity reaction develop, discontinue use immediately and initiate appropriate treatment. Ocular effects → advise patients to report any new-onset or worsening eye symptoms.
Black Box Warning	N/A
REMS*	N/A

Health Technology Assessment (HTA)

The below table lists the health technology Assessment recommendations for Tralokinumab by the Haute Autorite de Sante (HAS).

Table 28. Tralokinumab HTA Analysis

Medication	Agency	Date – HTA Recommendation
Tralokinumab	HAS[12]	2021: **Favorable opinion** for reimbursement in the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy in the event of failure, intolerance, or contraindication to ciclosporin. **Unfavorable opinion** for reimbursement following the failure of topical treatments in ciclosporin-naive patients, in the absence of comparative data.
	CADTH[14,15]	2022: The CADTH Canadian Drug Expert Committee (CDEC) recommends that tralokinumab **not be reimbursed** for the treatment of moderate to severe atopic dermatitis (AD) in adult patients. Evidence from 3 clinical trials showed that after 16 weeks of treatment, Adtralza was only modestly effective in reducing AD symptoms, including eliminating (or almost eliminating) skin lesions, alleviating itchy skin, and improving quality of life. These modest effects were shown when Adtralza was

		used alone or in combination with a topical corticosteroid. In another clinical trial in patients with severe AD, Adtralza in combination with topical corticosteroids effectively improved the Eczema Area and Severity Index (EASI) score (a tool used to measure the extent and severity of disease), but this effect was modest. In this same study, treatment with Adtralza in combination with topical corticosteroids did not significantly improve itchy skin than placebo in combination with topical corticosteroids. 2023: **Under process**
	IQWIG[13]	2023: No suitable data are available for the assessment of the added benefit of tralokinumab in comparison with the ACT in adolescents 12 years and older with moderate-to-severe atopic dermatitis who are candidates for systemic therapy. This results in no hint of an added benefit of tralokinumab in comparison with the ACT; an added benefit is therefore not proven.
	NICE	N/A
	PBAC	N/A

Conclusion Statement – Tralokinumab

Tralokinumab is a biologic drug approved by the FDA for adults (18+ years) with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies used on the skin (topical therapies) or when those therapies are not advisable.[34] The recommended dose is SUBQ: 600 mg (given as four 150 mg injections) once, followed by 300 mg (given as two 150 mg injections) once every other week. According to HAS, tralokinumab has a positive recommendation for treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy in the event of failure, intolerance, or contraindication to ciclosporin but a negative recommendation following the failure of topical treatments in ciclosporin-naive patients, in the absence of comparative data. According to CADTH, tralokinumab should not be re-imbursed but another CADTH HTA is under process right now. According to IQWIG, there is no added clinical benefit with Tralokinumab.

2.2 Modifications

Please refer to section 2.3.7 in the previous report:

- Pimecrolimus does not need “Prior Authorization (PA)” as a prescribing edit.

Please refer to section 2.3.7 in the previous report:

- Mupirocin, fusidic acid, cephalexin, acyclovir, ketoconazole, ciclopirox, fluconazole and itraconazole do not need “PA” as a prescribing edit.

Please refer to section 2.5.7 in the previous report:

- Cyclosporin, azathioprine, methotrexate and mycophenolate do not need “PA” as a prescribing edit.

Please refer to section 2.6.7 in the previous report:

- Dupilumab needs “PA”: This drug should be given for patients older than 6 months of age with moderate to severe AD in whom it is difficult to induce or maintain remission by topical therapy at 600mg once followed by 300mg once every other week after the failure of topical corticosteroids prescribed by a specialized immunosuppressants physician.

2.3 Delisting

The medications below are no longer SFDA registered (SFDA Drug List, July 2023), therefore, it is advisable to delist the following drugs from CHI formulary.

Alclomethasone and **Flumetasone**.

2.4 Other Drugs

2.4.1 Delgocitinib

Delgocitinib is still in Phase III clinical trials and the FDA has granted Delgocitinib Fast Track designation for topical treatment of adults with moderate to severe chronic hand eczema[38]. EMA approved delgocitinib in November 2021[39,40].

According to the clinical practice guidelines for the management of atopic dermatitis 2021, Delgocitinib ointment is recommended for patients with AD aged ≥2 years. Recommendation grade 1, Evidence level A[16].

2.4.2 Abrocitinib

Abrocitinib was approved by the FDA in January 2022[41], and by the EMA in December 2021[41]. Abrocitinib is approved for atopic dermatitis, refractory, moderate to severe[42]. It is not recommended for use with biologic immunomodulators, other Janus kinase inhibitors, or other systemic immunosuppressants. May be used with or without topical corticosteroids.

Oral:

- US labeling: Initial: 100 mg once daily. For insufficient response after 12 weeks, may increase dose to 200 mg once daily. Discontinue treatment if inadequate response is seen after dose increase.
- Canadian labeling: Initial: Adults <65 years of age: 100 to 200 mg once daily; in patients taking 200 mg once daily, consider decreasing dose to 100 mg once daily if symptom control is achieved by week 12; may increase back to 200 mg once daily if symptom control cannot be maintained up to a maximum dose of 200 mg/day[42].

2.4.3 Ruxolitinib cream

Ruxolutinib cream was FDA approved in July 2022[41], and EMA in February 2023[41].

Ruxolitinib is approved for atopic dermatitis, mild to moderate in the dosage form of cream. It should be applied as a thin layer to affected area(s) twice daily; application area should not exceed 20% BSA. Maximum dose: 60 g per week or 100 g per 2 weeks. Discontinue when signs/symptoms resolve. Reassess therapy if signs/symptoms have not resolved within 8 weeks[43].

2.4.4 Rocatinlimab

Currently under phase 3 trials, rocatinlimab is **not yet approved** for the treatment of moderate to severe atopic dermatitis in combination with topical corticosteroid and/or topical calcineurin inhibitors. The name of the study is ROCKET-SHUTTLE. The estimated primary completion date is September 20th, 2024, and the estimated study completion date is December 12th, 2024. The population are adults 18 years and older, therefore this drug is only studied in adults[44].

Section 3.0 Key Recommendations Synthesis

- TCS appear to be effective for AD, thus they are recommended if used appropriately and potential side effects are considered. (Recommendation grade 1, Evidence level A) [16]
- Topical tacrolimus is recommended for patients with AD aged ≥2 years. (Recommendation grade 1, Evidence level A) [16]
- Delgocitinib ointment is recommended for patients with AD aged ≥2 years. (Recommendation grade 1, Evidence level A) [16]
- The subcutaneous injection of dupilumab is recommended as remission induction and maintenance therapy for patients with moderate-to-severe AD in whom it is difficult to induce or maintain remission by topical therapy. (Recommendation grade 1, Evidence level A) [16]
- Baricitinib may be orally administered to patients with moderate to-severe AD in whom it is difficult to induce or maintain remission by topical therapy. (Recommendation grade 1, Evidence level A) [16]
- Tralokinumab is a biologic drug approved by the FDA for adults (18+ years) with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies used on the skin (topical therapies) or when those therapies are not advisable.[34]
- Upadacitinib is an oral JAK1 inhibitor approved by the FDA and EMA for adults and adolescents aged 12+ years with moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable.[30]
- In AD patients who are not adequately controlled with topical therapy or systemic therapies, the preferred systemic agent for use either alone or in combination with topical treatments is dupilumab, cyclosporine, methotrexate, phototherapy, or other available systemic treatments. (100% agreement).[21]

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Eczema report** and aims to provide recommendations to aid in the management of Eczema. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Eczema. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Eczema Scope

Section	Rationale/Updates
English Version of Clinical Practice Guidelines for the Management of Atopic Dermatitis 2021[16]	- TCS appear to be effective for AD, thus they are recommended if used appropriately and potential side effects are considered. Recommendation grade 1, Evidence level A. - It is desirable to reduce the application frequency of TCS and shift to a moisturizer after the disappearance of eruption in patients with moderate-to-severe AD who may experience relapses. Evidence level C. - The use of topical antimicrobial drugs for reducing the skin symptoms of AD is not recommended. Evidence level A.

	- Topical tacrolimus is recommended for patients with AD aged ≥2years. Recommendation grade 1, Evidence level A - Delgocitinib ointment is recommended for patients with AD aged ≥2years. Recommendation grade 1, Evidence level A. - Antihistamines may reduce itching symptoms when used in combination with anti-inflammatory topical drugs and topical moisturizing drugs, therefore their use is proposed as an “add-on” therapy to topical anti-inflammatory treatment for AD. Non sedative second-generation antihistamines should be selected. Recommendation grade 2, Evidence level B. - Proactive therapy is an effective treatment to maintain remission of eczema lesions and is a relatively safe treatment. Recommendation grade 1, Evidence level A. - The use of topical moisturizing agents is recommended for dermatitis in combination with TCS or topical tacrolimus. The continuous use of a topical moisturizer is recommended even after reducing symptoms of dermatitis during the acute phase. Recommendation grade 1, Evidence level A. - Currently, the application of moisturizers in neonates for the prevention of AD onset is not unconditionally recommended. Recommendation grade 2, Evidence level B. - For patients with AD in whom control is difficult, despite the application of TCS or tacrolimus, skin care, and elimination of triggering factors, cyclosporin therapy may be selected. Recommendation grade 2, Evidence level A. - Phototherapy may be performed in patients in whom the relief of AD is not achieved by topical therapy, skin care, or strategies to avoid exacerbating factors or in patients with moderate-to-severe AD with adverse reactions to conventional treatment. Recommendation grade 2, Evidence level B. - The subcutaneous injection of dupilumab is recommended as remission induction and maintenance therapy for patients with moderate-to-severe AD in whom it is difficult to induce or maintain remission by topical therapy. Recommendation grade 1, Evidence level A. - Baricitinib may be orally administered to patients with moderate to-severe AD in whom it is difficult to induce or maintain remission by topical therapy. Recommendation grade 1, Evidence level A. - Currently, neither probiotics/prebiotics nor synbiotics in which both are combined are recommended to reduce AD symptoms. Evidence level B. - The administration of probiotics or prebiotics for the prevention of AD onset is not recommended. Evidence level B.

	- Many epidemiological observational studies and meta-analyses have suggested that the administration of antihistamines during pregnancy does not increase the incidence of congenital anomalies, but the evidence is insufficient. If the therapeutic advantage of administration is great, drugs that are reported to be safe may be administered after receiving informed consent by explaining the risk in comparison with the incidence of malformations as a background (2–3%). Although very small amounts of drug are transferred to breastmilk, package inserts of most drugs state avoidance of breastfeeding; caution is thus needed. Regarding individual drugs, careful consideration of the contents of package inserts and the latest information on safety profiles is also necessary. Evidence level B. - The use of TCS according to standard methods during pregnancy or lactation is safe. They may be used without worrying about their influence on fetuses or infants. However, the use of high dose potent topical steroids for extended periods should be avoided because these may cause low weight at birth. Evidence level B. - Soap and detergents may be useful for the management of AD if specific skin conditions, type of soap and detergent, and cleaning methods are considered. Recommendation grade 1, Evidence level C. - No medical evidence actively recommends the use of povidoneiodine solution. It may be considered an adjuvant therapy for cases that are difficult to treat using first line TCS because of infection, but povidone-iodine should not be used without careful consideration of safety concerns. Evidence level C.
Japanese guidelines for atopic dermatitis 2020[19]	- TCS are often used as a first-line anti-inflammatory topical agent for both children and adults. N/A - Selection of rank. In Japan, TCS are generally classified into 5 ranks: strongest (Group 1), very strong (Group 2), strong (Group 3), medium (Group 4), and weak (Group 5) (Table 3). It is important to adequately select drugs at a rank that matches the severity of each eruption and use them at the required volume for the required period. ➔ **Insert 2 tables.** ➔ **Insert figure.**
European task force on atopic dermatitis position paper: treatment of parental atopic	This guideline targets treatment in pregnant population.

dermatitis during preconception, pregnancy, and lactation period[20]	
German S1 guidelines for the diagnosis and treatment of perianal dermatitis (anal eczema)[17]	<u>Nonpharmacological treatment of perianal dermatitis includes the following aspects:</u> - Optimized anal hygiene - Detergent-free cleansing with tepid water (anal douching or sitz baths) - Gentle drying with cotton pads, soft towels, or unbleached, fragrance-free paper towels - Optimized bowel movement habits - Dietary modifications aimed at achieving formed stool If applicable: reduction in the frequency of bowel movements If applicable: supplemental intake of bulking agents (e.g., psyllium) -Skin care and protection -Gentle, allergen-free skin care products (e.g., hydrophilic oil-in-water preparations) -Skin protection with zinc oxide paste - Use of loose cotton underwear (to avoid constriction) A topical anti-inflammatory treatment is recommended in the following circumstances: - In cases marked by highly inflammatory lesions to ensure rapid symptom relief. -Whenever treatment or elimination of causative factors as well as nonpharmacological measures have failed or are insufficiently effective. In cases of bacterial or fungal superinfection or pathogen-induced perianal dermatitis, appropriate topical and/or systemic treatments shall be initiated: -Bacterial superinfection (impetiginization) – Preferential use of antiseptics – Topical bacteriostatic or bactericidal agents can be used alone or in combination with topical corticosteroids – Depending on the clinical situation, use of systemic antibiotics must be considered } Fungal superinfection: – Topical antifungals can be used alone or, in case of severe inflammatory lesions, in combination with topical corticosteroids – Depending on the causative agent (trichophytes, epidermophytes, candida), antifungal agents with varying spectra of activity may be used

Appendix C. MeSH Terms PubMed

Query	Filters	Search Details	Results
(((((Eczema [MeSH Terms]) OR (Eczemas[Title/Abstract])) OR (Dermatitis, Eczematous[Title/Abstract])) OR (Dermatitides, Eczematous[Title/Abstract])) OR (Eczematous Dermatitides[Title/Abstract])) OR (Eczematous Dermatitis[Title/Abstract])	Guideline, in the last 5 years	("eczema"[MeSH Terms] OR "Eczemas"[Title/Abstract] OR "dermatitis eczematous"[Title/Abstract] OR (("dermatiti"[All Fields] OR "Dermatitis"[MeSH Terms] OR "Dermatitis"[All Fields] OR "Dermatitides"[All Fields]) AND "Eczematous"[Title/Abstract]) OR "eczematous dermatitides"[Title/Abstract] OR "eczematous dermatitis"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline [Filter]))	3
((((((((((((((Dermatitis, Atopic[MeSH Terms]) OR (Atopic Dermatitides[Title/Abstract])) OR (Atopic Dermatitis[Title/Abstract])) OR (Dermatitides, Atopic[Title/Abstract])) OR (Neurodermatitis, Atopic[Title/Abstract])) OR (Atopic Neurodermatitides[Title/Abstract])) OR (Atopic Neurodermatitis[Title/Abstract])) OR (Neurodermatitides, Atopic[Title/Abstract])) OR (Neurodermatitis, Disseminated[Title/Abstract])) OR (Disseminated Neurodermatitides[Title/Abstract])) OR (Disseminated Neurodermatitis[Title/Abstract])) OR (Neurodermatitides, Disseminated[Title/Abstract]))	Guideline, in the last 5 years	("dermatitis, atopic"[MeSH Terms] OR (("Atopic"[All Fields] OR "atopical"[All Fields] OR "atopics"[All Fields]) AND "Dermatitides"[Title/Abstract]) OR "atopic dermatitis"[Title/Abstract] OR (("dermatiti"[All Fields] OR "Dermatitis"[MeSH Terms] OR "Dermatitis"[All Fields] OR "Dermatitides"[All Fields]) AND "Atopic"[Title/Abstract]) OR "neurodermatitis atopic"[Title/Abstract] OR "atopic neurodermatitis"[Title/Abstract] OR (("Neurodermatitis"[MeSH Terms] OR "Neurodermatitis"[All Fields]) AND	20

OR (Eczema, Atopic[Title/Abstract])) OR (Atopic Eczema[Title/Abstract])) OR (Eczema, Infantile[Title/Abstract])) OR (Infantile Eczema[Title/Abstract])		"Atopic"[Title/Abstract]) OR "neurodermatitis disseminated"[Title/Abstract] OR "disseminated neurodermatitis"[Title/Abstract] OR (("Neurodermatitis"[MeSH Terms] OR "Neurodermatitis"[All Fields]) AND "Disseminated"[Title/Abstract]) OR "eczema atopic"[Title/Abstract] OR "atopic eczema"[Title/Abstract] OR "eczema infantile"[Title/Abstract] OR "infantile eczema"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithm