URTICARIA

CHI Formulary Indication Review

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Council of Health Insurance

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Table of Contents

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

List of Tables

List of Figures

Abbreviations

CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
IDF	Insurance Drug Formulary
IQWIG	Institute for Quality and Efficiency in Health Care
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
ED	Emergency department
ESR	Erythrocyte Sedimentation Rate
CRP	C-Reactive Protein
AEDV	Academy of Dermatology and Venereology
AAFP	American Academy of Family Physicians
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
CU	Chronic Urticaria
CSU	Chronic spontaneous Urticaria
TFDA	Taiwan Food and Drug Administration
UAS	Urticaria Activity Score
UCT	Urticaria Control Test
BHRA	Basophil Histamine Release Assay
ASSTS	Autologous Serum Skin Tests
CUA	Chronic Urticaria and Angioedema

Executive Summary

Urticaria, or hives (sometimes referred to as welts or wheals), is a common disorder, with a lifetime prevalence of approximately 20% in the general population. In the Kingdom of Saudi Arabia (KSA), survey-based results on the epidemiology of urticaria among adults showed that 19.8% of responders (166 out of 838) experienced any of the urticaria clinical presentations while 80.2% never experienced any. Urticaria was significantly more reported among females, with 25.3% compared to 14.9% of males. 19.9% of patients with history of urticaria complained of angioedema[1].

Urticaria can also have an impact on the patient's quality of life. A descriptive cross-sectional study conducted in Jeddah city looked at the dermatology life quality index (DLQI) in patients with chronic idiopathic urticaria. It found that the majority of patients (51%) reported DLQI scores between 11 and 20, meaning the disease has a very large effect on their life[2].

A typical urticarial lesion is an intensely pruritic, erythematous plaque (figure 1). Urticaria is sometimes accompanied by angioedema, which is swelling deeper in the skin. A presumptive trigger, such as a drug, food ingestion, insect sting, or infection, may be identifiable in patients with new onset urticaria, although no specific cause is found in many cases, particularly when the condition persists for weeks or months[3,4].

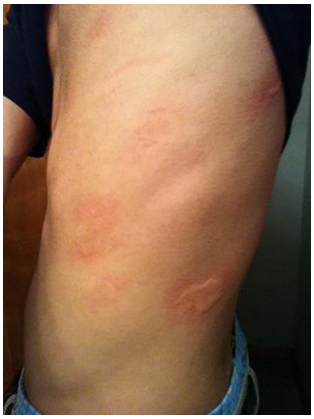


***Figure 1**. Acute urticaria on the trunk.*

Urticaria (with or without angioedema) is commonly categorized by its chronicity:

- **Acute urticaria**: present for less than six weeks.
- **Chronic urticaria**: recurrent, with signs and symptoms recurring most days of the week, for six weeks or longer.

The period of six weeks is somewhat arbitrary and simply represents a timeframe in which new cases of urticaria usually resolve. More than two-thirds of cases of new-

onset urticaria prove to be self-limited (acute). The lesions of acute and chronic urticaria are identical in appearance, so when the problem first develops, it is not possible to differentiate the two disorders[3,4].

Urticarial lesions are circumscribed, raised, erythematous plaques, often with central pallor. Lesions may be round, oval, or serpiginous in shape and vary in size from less than 1 centimeter to several centimeters in diameter. They are intensely itchy. Pruritus may disrupt work, school, or sleep. Symptoms often seem most severe at night.

Individual lesions are transient, usually appearing and enlarging over the course of minutes to hours and then disappearing within 24 hours. Lesions may coalesce as they enlarge. Urticarial lesions are not normally painful and resolve without leaving residual ecchymotic marks on the skin unless there is trauma from scratching.

Any area of the body may be affected, although areas in which clothing compresses the skin (e.g., under waistbands) or skin rubs together (axillae) are sometimes affected more dramatically. Typically, compressed areas become more severely affected once the restricting clothing has been removed.

Urticaria is diagnosed clinically, based upon a detailed history and physical examination confirming the presence of characteristic skin lesions.

Lesions should be visualized directly in order to make the diagnosis with certainty, since the term "hives" is used nonspecifically by patients. If the patient has no lesions at the time of evaluation, showing patients photographs of urticaria and asking if their lesions look similar can be helpful, although the diagnosis will need to be confirmed at some point in the future.

Individual wheals (hives) typically clear within 24 hours without treatment; however, angioedema may take up to 72 hours to resolve. Typically, the hives (urticarial lesions) do not remain after the symptoms resolve. Excoriation may be present due to scratching of the lesions. With acute urticaria, wheals can recur for up to 6 weeks, depending on the cause. For chronic urticaria, urticarial flare-ups reoccur more days than not, for more than 6 weeks.

The most reported triggers/risk factors of initiating urticaria symptoms were skin itching (68%), followed by spontaneously or no reason (57%).

Timely transport to the emergency department (ED) for any patient with signs or symptoms of a life-threatening allergic reaction, including urticaria (hives), angioedema, or anaphylactic shock is essential. Acute urticaria may progress to life-threatening angioedema and/or anaphylactic shock in a very short period, although anaphylaxis usually presents as rapid-onset shock with no urticaria or angioedema.

To assess the disease activity, the Urticaria Activity Score (UAS) system and the Urticaria Control Test (UCT) can be used. In both clinical practice and medical trials,

the UAS system is the recommended method for assessing disease activity in chronic spontaneous urticaria (CSU). More specifically, the Urticaria Activity Score for 7 days is the standard used by the EAACI for such evaluations. The UAS system provides two distinct advantages:

- Due to widespread adaptation, the use of the UAS system allows for a direct comparison of study and results from various researchers worldwide;
- The UAS system is based on the patient's own assessment of key symptoms such as wheals and pruritus, and this self-assessment is particularly valuable because the intensity of urticaria symptoms changes often, such that the 24-h self-evaluation scores taken once daily by the patient for several days provide the best picture of the overall disease activity.

Recently, the UCT (figure 2) has become valuable in the assessment of patients' disease status and has been validated to determine the level of disease control in all forms of CU. The UCT has only four items with a clearly defined cut-off for patients with "well-controlled" vs. "poorly controlled" disease. It is, thus, suited for the management of patients in routine clinical practice. The cut-off value for a well-controlled disease is 12 of 16 points. This helps to guide treatment decisions.

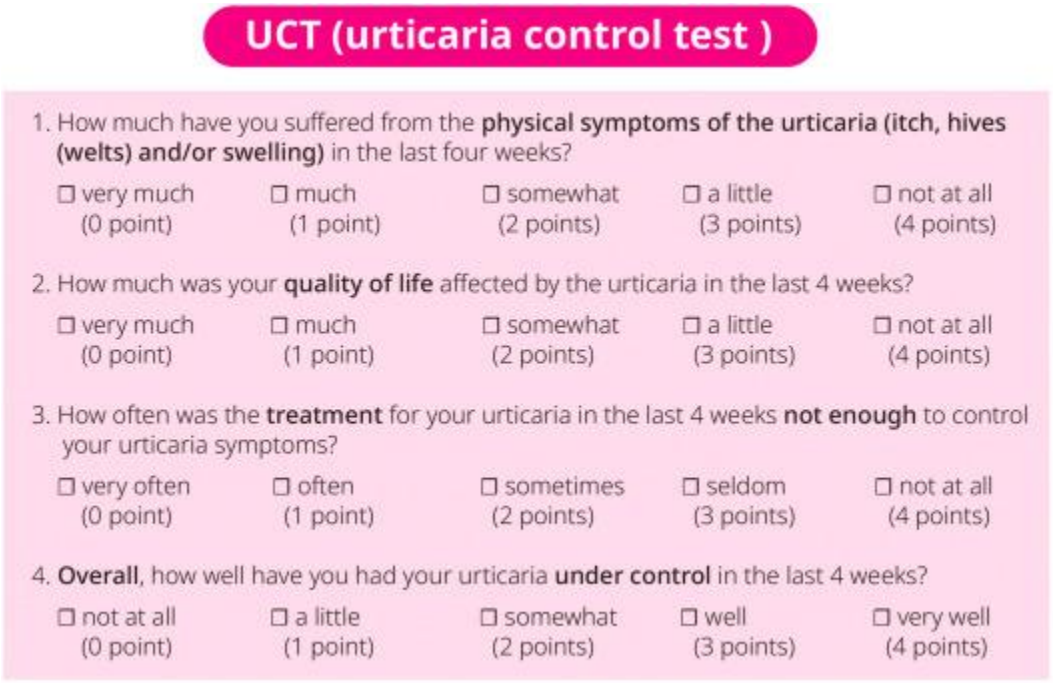


Figure 2. *The Urticaria Control Test (UCT) for assessing disease status and determine the level of disease control in all forms of chronic urticaria.*

Initial treatment of urticaria should focus on the short-term relief of pruritus and angioedema if present. **H1-antihistamines are first-line pharmacotherapy.** Second-generation H1 antihistamines are relatively nonsedating at standard dosages and are

dosed once per day. If symptoms are not sufficiently controlled with second-generation H1 antihistamines, **H2 antihistamines** such as famotidine or cimetidine may be added. In severe cases, **corticosteroids** such as prednisone may be added for three to 10 days to control symptoms[3]. **Omalizumab**, a recombinant humanized monoclonal antibody against IgE, is approved for the treatment of antihistamine-refractory chronic urticaria. Immunosuppressants such as cyclosporine also play a role in the management. Novel therapies under development include the anti-IgE ligelizumab that works with a much higher affinity than omalizumab, as well as the bruton tyrosine kinase (BTK) inhibitors fenebrutinib, remibrutinib, and rilzabrutinib. Studies are also ongoing to evaluate the role of the anti-interleukin-5 (anti-IL5) monoclonal antibodies mepolizumab, reslizumab, and benralizumab, the thymic stromal lymphopoietin (TSLP) blocker tezepelumab, and the anti-Siglec-8 monoclonal antibody lirentelimab[5].

This report compiles all clinical and economic evidence related to Urticaria according to the relevant sources. The ultimate objective of issuing urticaria guidelines by the Council of Health Insurance is to update the IDF (CHI Drug Formulary) with **the best available clinical and economic evidence related to drug therapies, ensuring timely and safe access to patients with urticaria in Saudi Arabia**. The main focus of the review was on North American and European and other international guidelines issued within the last five years. To elaborate, North American guidelines detailed the management of acute and chronic urticaria. Furthermore, European and international guidelines elaborated on the diagnosis, classification and the management of urticaria in special population (elderly patients, patients with renal and hepatic impairment, pediatric patients, pregnant and breastfeeding women).

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in urticaria were reviewed and summarized under each drug therapy table in Section 2.0. 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).

Section 2.0 provides a full description of each pharmacological agent with final statements on the placement of therapy. All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of urticaria.

Major recommendations for suggested drug therapies are summarized in the table below:

Table 1. SFDA-Registered Drugs for the Management of Urticaria

Medication	Indication	Line of Therapy	Level of Evidence/ Recommendation	HTA Recommendations
Desloratadine	Urticaria	**1st**	Grade 2B	N/A
Loratadine	Urticaria	**1st**	Grade 2B	N/A
Fexofenadine	Urticaria	**1st**	Grade 2B	N/A
Cetirizine	Urticaria	**1st**	Grade 2B	Positive Recommendation from NICE
Levocetirizine	Urticaria	**1st**	Grade 2B	N/A
Famotidine	If symptoms are not sufficiently controlled with second-generation H1 antihistamines.	**2nd**	No Grade	N/A
Prednisone	If symptoms are not sufficiently controlled with second-generation H1 antihistamines.	**3rd**	Grade 2C	N/A
Montelukast	If symptoms are not sufficiently controlled with second-generation H1 antihistamines.	**3rd**	No Grade	N/A
Hydroxyzine	If symptoms are not sufficiently controlled with H2 antihistamines, hydroxyzine may be added	**3rd**	No Grade	N/A

Omalizumab	Urticaria (For patients who do not respond well to antihistamines)	**3rd**	No Grade	Positive Recommendation from NICE, CADTH, and HAS
Cyclosporin	Urticaria (For patients who do not respond well to antihistamines)	**4th**	No Grade	N/A
Epinephrine	In urticaria, after H1 and H2 antihistamines and systemic steroids for severe angioedema	**3rd**	No Grade	N/A

Table 2. Non-SFDA-Registered Drugs for the Management of Urticaria

Medication	Indication	Line of Therapy	Level of Evidence/Recommendation
Zafirlukast	Patients with NSAID intolerance or cold urticaria	**2nd**	N/A
Doxepin	Urticaria	**3rd**	N/A

The report concludes with the addition of a key recommendation synthesis section, which emphasizes the utilization of each drug class for specific patient groups.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

1.1 KSA Guidelines

To date, no guidelines have been published by Saudi bodies for the management of urticaria.

1.2 North American Guidelines

1.2.1 American Academy of Family Physicians (AAFP) Guidelines for the Management of Acute and Chronic Urticaria (2017)

The American Academy of Family Physicians (AAFP) published its clinical guidelines for the diagnosis, treatment, and follow-up of urticaria in 2017. The following guideline does not provide a specified grade of evidence or level of recommendation[6].

Definition

- Urticaria is a common dermatologic condition that typically presents with intensely pruritic, well-circumscribed, raised wheals ranging from several millimeters to several centimeters or larger in size.
- Urticaria can occur with angioedema, which is localized nonpitting edema of the subcutaneous or interstitial tissue that may be painful and warm.
- Typically otherwise benign and self-limited, urticaria can be a symptom of life-threatening anaphylaxis or, rarely, indicate significant underlying disease.
- Urticaria can appear on any part of the skin. The wheals can be pale to brightly erythematous in color, often with surrounding erythema. The lesions are round, polymorphic, or serpiginous, and can rapidly grow and coalesce.
- Angioedema presents primarily in the face, lips, mouth, upper airway, genitalia, and extremities. The onset of symptoms for urticaria or angioedema is rapid, usually occurring over minutes.
- Individual urticarial lesions typically resolve in one to 24 hours without treatment, although additional wheals can erupt in new crops. Angioedema may take days to resolve. Urticaria, with or without angioedema, can be classified as acute or chronic.

- Urticaria that recurs within a period of less than six weeks is acute. Recurring chronic urticaria lasts longer than six weeks. Urticaria can present in persons of any age, with a lifetime prevalence of approximately 20%. Chronic urticaria has a lifetime prevalence of approximately 0.5% to 5%.

Diagnosis

- The diagnosis of urticaria is usually clinical. The first step in evaluating urticaria is a history and physical examination to characterize the lesions and help identify causes.
- History elements that should be elicited include onset, timing (e.g., with the menstrual cycle, if an association is suspected), location, and severity of symptoms; associated symptoms, which may suggest anaphylaxis; and potential environmental triggers. Other important parts of the history include medication and supplement use, (especially new or recently changed dosages), allergies, recent infections, family history of urticaria, and complete review of systems to identify possible causes and symptoms of systemic illnesses.
- The physical examination should include vital signs, identification and characterization of current lesions and their complete extent, testing for dermatographism and cardiopulmonary examination to help rule out anaphylaxis and infectious causes. Examination of the eyes, ears, nose, throat, lymph nodes, abdomen, and musculoskeletal system may help identify underlying causes.
- Table 3 lists clinical clues from the history and physical examination that suggest certain etiologies for urticaria. It is critical to rule out anaphylaxis, which has findings or symptoms involving other organ systems beyond the skin, such as the pulmonary (wheezing, stridor), cardiovascular (tachycardia, hypotension), gastrointestinal (diarrhea, vomiting, abdominal pain), or nervous system (dizziness).

Table 3. Urticaria-Associated History and Physical

Clinical clue	Possible etiology
Abdominal pain, dizziness, hypotension, large erythematous patches, shortness of breath, stridor, tachycardia	Anaphylaxis
Dermatographism, physical stimuli	Physical urticaria
Food ingestion temporally related to symptoms	Food allergy

High-risk sexual behavior or illicit drug use history	Hepatitis B or C (cryoglobulinemia) virus, human immunodeficiency virus
Infectious exposure, symptoms of upper respiratory tract or urinary tract infections	Infection
Joint pain, uveitis, fever, systemic symptoms	Autoimmune disease
Medication use or change	Medication allergy or direct mast cell degranulation
Pregnancy	Pruritic urticarial papules and plaques of pregnancy
Premenstrual flare-up	Autoimmune progesterone dermatitis
Smaller wheals (1 to 3 mm); burning or itching; brought on by heat, exercise, or stress	Cholinergic urticaria
Thyromegaly, weight gain, cold intolerance	Hypothyroidism
Travel	Parasitic or other infection
Weight loss (unintentional), fevers, night sweats	Lymphoma
Wheals lasting longer than 24 hours, nonblanching papules, burning or other discomfort, residual hyperpigmentation, fevers, arthralgias	Urticarial vasculitis

General principles of treatment of acute urticaria

- Methods of treatment for urticaria are the same for adults and children.
- The mainstay of treatment is avoidance of identified triggers. It is also recommended that patients avoid using aspirin, alcohol, and non-steroidal anti-inflammatory drugs (NSAIDs), as well as avoid wearing tight clothing, because these may worsen symptoms.
- If trigger avoidance is impossible, no trigger is identified, or symptom relief is needed despite trigger avoidance, **H1-antihistamines are first-line pharmacotherapy.** Second-generation H1 antihistamines such as loratadine, desloratadine, fexofenadine, cetirizine and levocetirizine are relatively nonsedating at standard dosages and are dosed once per day. First-generation H1 antihistamines are faster acting and, in some cases, have

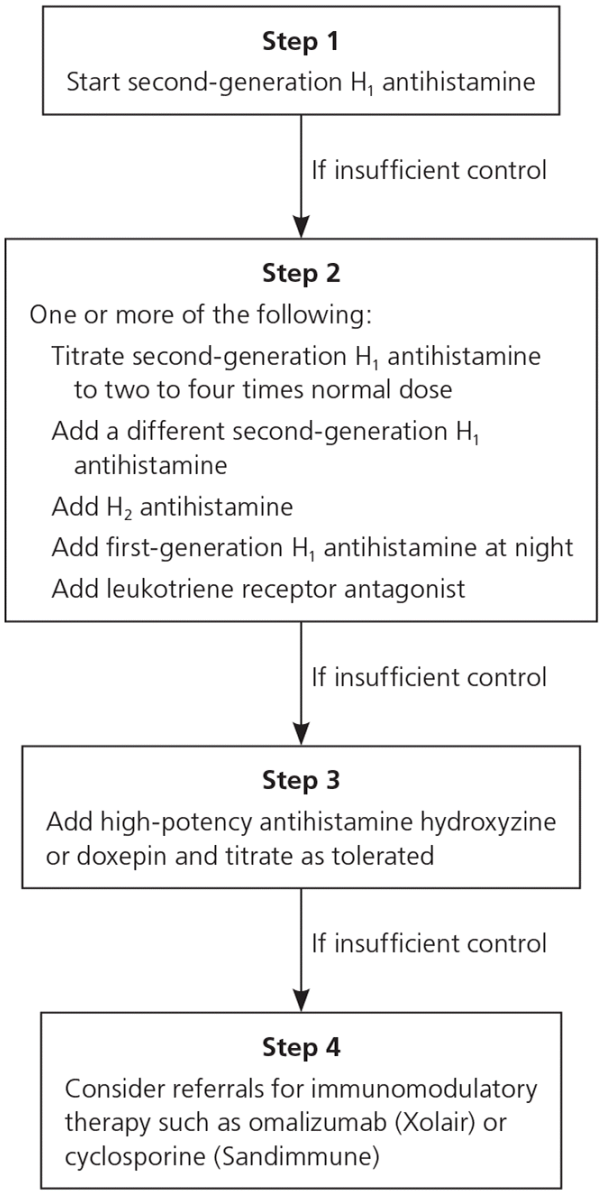
parenteral forms. However, they require more frequent dosing and have more adverse effects, including sedation, confusion, dizziness, impaired concentration, and decreased psychomotor performance. Because of anticholinergic adverse effects, first-generation H1 antihistamines should be used with caution in older patients.

- There is no strong evidence that a particular antihistamine is superior.
- If symptoms are not sufficiently controlled with second-generation H1 antihistamines, **H2 antihistamines** such as famotidine, ranitidine and cimetidine may be added. In severe cases, **corticosteroids** such as prednisone (0.5 to 1 mg per kg per day) may be added for three to 10 days to control symptoms.
- If systemic symptoms are suggested, especially when an identified trigger is associated with anaphylaxis (e.g., insect envenomation, certain foods), it may be prudent to prescribe **epinephrine autoinjectors** in sufficient numbers so that the patient will have one for home, one for work or school, and one for the car, as appropriate.
- Patients should follow up in two to six weeks to evaluate treatment success and tolerance.

General principles of treatment of chronic urticaria

- Current guidelines suggest a stepwise approach to treating chronic idiopathic urticaria (figure 2). As with acute urticaria, the first step is **second generation H1 antihistamines**. For improved symptom control, the medication should be dosed daily, rather than on an as-needed basis.
- The American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology recommend that if first-line treatment is insufficient, the second step is implementation of one or more of the following additional strategies: the second-generation H1 antihistamine can be titrated up to two to four times the usual dose; a different second generation H1 antihistamine can be added; first-generation H1 antihistamines may be added at night-time; **H2 antihistamines** may be added; and **leukotriene receptor antagonists**, such as montelukast and zafirlukast, can also be added, especially in patients with NSAID intolerance or cold urticaria.
- If symptomatic control is still not achieved, the third step is addition and titration of **high-potency antihistamines** as tolerated, such as hydroxyzine or the tricyclic antidepressant doxepin (possesses markedly more antihistaminic effect than diphenhydramine).

- The fourth step is referral to a subspecialist for use of **immunomodulatory agents**. There are a number of such agents, but the data on the effectiveness in chronic urticaria for most are weak at best. The two agents with the most robust data are omalizumab and cyclosporine.
- For controlling flare-ups in chronic urticaria, a three to 10 day burst of corticosteroids (prednisone up to 1 mg per kg per day) is sometimes used; long-term use is not recommended because of adverse effects. Potent topical corticosteroids may have a benefit in localized delayed-pressure urticaria. Once symptoms are adequately controlled, physicians should consider stepping down treatment sequentially.
- If an underlying cause of chronic urticaria is identified, the condition should be treated or the patient referred to an appropriate subspecialist.



NOTE: *If symptoms are severe, a short course (3 to 10 days) of systemic corticosteroids (e.g., oral prednisone, 0.5 to 1 mg per kg per day) may be added at steps 1, 2, or 3.*

Figure 3. *Stepwise Treatment of Chronic Urticaria*

1.2.2 American Academy of Allergy, Asthma, and Immunology (AAAAI) Guidelines for the Management of Acute and Chronic Urticaria (2014)

The American Academy of Allergy, Asthma, and Immunology (AAAAI) published its clinical guidelines for the diagnosis, treatment, and follow-up of urticaria in 2014[7,8]. A summary of the recommendations can be found below:

Management of Chronic Urticaria (CU)

Management of CU involves both nonpharmacologic and pharmacologic approaches. Nonsteroidal anti-inflammatory drugs, heat, and tight clothing might exacerbate CU in some patients, and avoidance of these factors might be beneficial. Pseudoallergens have been defined as substances that can induce intolerance reactions and include food additives, vasoactive substances, fruits, vegetables, and spices. The utility of a pseudoallergen-free diet for management of CU has not been convincingly demonstrated. Avoidance of pseudoallergens in the diet is not recommended. Potent topical corticosteroids might improve symptoms from delayed-pressure urticaria but have limited utility in the treatment of diffuse CU.

1. **Monotherapy with second-generation antihistamines**

   H1-antagonists are effective in the majority of patients with CU but might not achieve complete control in all patients. Second-generation antihistamines are generally tolerated without remarkable untoward effects.

2. **Dose advancement of H1-antihistamine therapy, combining first- and second-generation agents and adding an H2-antihistamine and/or an antileukotriene agent**

   Higher doses of second-generation antihistamines can provide greater efficacy when control is not achieved with conventional doses of these agents, either alone or in combination. Efficacy of first-generation antihistamines is similar to that of second-generation antihistamines, but sedation and impairment are greater with first- generation antihistamines, especially with short-term use. A 2- to 4-fold increase in the FDA-approved dose of second-generation antihistamines might be effective for achieving control in some patients.

   There are no comparative studies that have examined the relative effectiveness of adding an H2-antihistamine compared with an antileukotriene drug or an H1-antihistamine at bedtime. H2-antagonists have shown benefit in combination with first-generation antihistamines for the treatment of CU. However, the efficacy of H2-antagonists in patients with CU might be related to pharmacologic interaction and increased blood levels of

first-generation antihistamines. Some, but not all, studies have found leukotriene receptor antagonists to have efficacy in patients with CU.

3. **Therapeutic trial of potent antihistamine (doxepin)**

   Doxepin, advanced as tolerated, has potent H1- and H2-antagonist activity and is efficacious. Although the degree of impairment varies among first-generation antihistamines, as a group, they cause significantly greater impairment of cognition and psychomotor function than second-generation antihistamines. For this reason, first-generation antihistamines should be prescribed cautiously in the elderly or patients with occupations (eg, machine operators, airline pilots, or alpine skiers) for which alertness is essential.

4. **Add an immunosuppressant or biologic agent**

   Multiple factors are involved in selecting an alternative agent in patients with refractory CU, including, but not limited to, the presence of comorbid factors, frequency of treatment-related visits, cost, rapidity of response, adverse effects, and the patient's values and preferences. The potential risk of a given alternative agent is extremely important and needs to be weighed against the patient's current quality of life and any adverse effects from current therapy for their CU. A number of alternative therapies have been studied for the treatment of CU and merit consideration for refractory patients. Omalizumab and cyclosporine have the greatest published experience documenting efficacy in patients with CU compared with all other alternative agents.

H1-antihistamines

- H1-antagonists are effective in the majority of patients with CU but might not achieve complete control in all patients. (C)
- Second-generation antihistamines are safe and effective therapies in patients with CU and are considered first-line agents. (A)
- Higher doses of second-generation antihistamines might provide more efficacy, but data are limited and conflicting for certain agents. (B)
- First-generation antihistamines have proved efficacy in the treatment of CU. Efficacy of first-generation antihistamines is similar to that of second-generation antihistamines, but sedation and impairment are greater with first-generation antihistamines, especially with short-term use. (A) First-generation antihistamines can be considered in patients who do not achieve control of their condition with higher-dose second-generation antihistamines. (D)

H2-antihistamines

- H2-antihistamines taken in combination with first- and second-generation H1-antihistamines have been reported to be more efficacious compared with H1-antihistamines alone for the treatment of CU. (A)
- However, this added efficacy might be related to pharmacologic interactions and increased blood levels of first-generation antihistamines. (B)
- Because these agents are well tolerated, the addition of H2-antagonists can be considered when CU is not optimally controlled with second-generation antihistamine monotherapy. (D)
- H2-receptor antagonists have also been used to treat urticaria in conjunction with H1-receptor antagonists and are generally well tolerated.

Leukotriene modifiers

- Leukotriene receptor antagonists have been shown in several, but not all, randomized controlled studies to be efficacious in patients with CU. (A)
- Leukotriene receptor antagonists are generally well tolerated (A).
- Leukotriene receptor antagonists can be considered for patients with CU with unsatisfactory responses to second-generation antihistamine monotherapy.

Antidepressants with H1- and H2-antagonist activity: Doxepin

- Doxepin is a tricyclic antidepressant with both H1- and H2-receptor antagonist properties.
- Treatment with doxepin can be considered in patients whose symptoms remain poorly controlled with dose advancement of second-generation antihistamines and the addition of H2-antihistamines, first-generation H1-antihistamines at bedtime, and/or antileukotrienes. (D)

Systemic corticosteroids

- Systemic corticosteroids are frequently used in patients with CU refractory to antihistamine therapy.
- Systemic corticosteroids are frequently used in patients with refractory CU, but no controlled studies have demonstrated efficacy. In some patients, short-term use (e.g., 1-3 weeks' duration) might be required to gain control of their symptoms until other therapies can achieve control.
- Because of the risk of adverse effects with systemic corticosteroids, long-term use for treatment of patients with CU should be avoided as much as possible. (D)

Immunosuppressant agents

- Several immunosuppressant agents have been used in patients with antihistamine-refractory CU. **Cyclosporine** has been studied in several randomized controlled trials. Taken in the context of study limitations, potential harms, and cost, the quality of evidence supporting use of cyclosporine for refractory chronic urticaria, and angioedema (CUA) is low. On the basis of current evidence, this leads to a weak recommendation for use of cyclosporine in patients with CUA refractory to conventional treatment. (A)
- Cyclosporine has been studied in several randomized controlled trials. For this reason, cyclosporine was selected for closer examination as to the quality of evidence supporting its administration in patients with refractory CU.
- Immunosuppressant agents have been associated with remission of CU in uncontrolled studies. (C) Use of immunosuppressant agents can be considered after analyzing the risks and benefits of therapy and should generally be reserved for more refractory patients, particularly those who require frequent or long-term corticosteroids for control of CU. (D)

Biologic agents: Omalizumab

- In contrast to other alternative agents for refractory CU, the therapeutic utility of omalizumab has been supported by findings from large double-blind, randomized controlled trials and is associated with a relatively low rate of clinically significant adverse effects. On the basis of this evidence, omalizumab should be considered for refractory CU if, from an individualized standpoint, a therapeutic trial of omalizumab is favorable from the standpoint of balancing the potential for benefit with the potential for harm/burden and cost and the decision to proceed is consistent with the patient's values and preferences. (A)

1.3 European Guidelines

1.3.1 Spanish Academy of Dermatology and Venereology (AEDV) Review of the Latest Recommendations on the Management of Chronic Urticaria (2019)

The Spanish consensus summarizes the European clinical guidelines for the management of chronic urticaria in 2019[9]. *The following guideline does not provide a specified grade of evidence or level of recommendation.*

Diagnosis

- The diagnostic workup should be based on patient history, physical examination, differential blood count and one of the 2 acute-phase factors: erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).
- History taking should focus on clinical factors associated with a poor prognosis, such as angioedema, inducible chronic urticaria (CU), association or worsening with NSAIDS, inadequate treatment response, and previous treatment failure.

Treatment

- According to the European guidelines, the goal of treatment should be to achieve complete control of physical signs and symptoms without compromising patient safety and quality of life.
- Treatment of chronic spontaneous urticaria (CSU) consists of avoidance of identified triggers and administration of drugs to control symptoms. The guidelines recommend **second-generation H1 antihistamines** as first-line therapy for symptom control in CSU. Approximately 50% of patients, however, remain symptomatic despite treatment with antihistamines.
- The recommended second-line strategy is to **increase the standard dose of antihistamines** up to 4-fold.
- If this fails, **omalizumab** and **ciclosporin A** can be added as third- and fourth-line options respectively.
- The guidelines recommend a short course of oral **corticosteroids** lasting no longer than 10 days for patients who experience exacerbations.

<u>Antihistamines</u>

- First-generation H1 antihistamines are not recommended for CU as they have poor selectivity, penetrate the blood-brain barrier, and have a high number of adverse effects. However second-generation antihistamines used continuously were the first-line therapy for CU, followed by antihistamines at 2 or 4 times the standard dose as second-line therapy.

<u>Omalizumab</u>

- The efficacy and safety of omalizumab for the treatment of CSU was demonstrated in the pivotal phase III clinical trials ASTERIA I, ASTERIA II, and GLACIAL. Omalizumab has also been shown to be effective and safe in real-world observational studies of patients with CSU, including a retrospective, descriptive study of 110 patients treated with omalizumab in 9 Spanish hospitals.

- Omalizumab was an effective treatment for all subtypes of urticaria and may be the treatment of choice for antihistamine-resistant patients. The recent results of the XTEND-CIU study on the use of omalizumab in CSU for over 6 months showed that continued treatment prevented recurrences, improved quality of life, and reduced the number of angioedema episodes.
- Long-term treatment with omalizumab is effective and safe.
- 300 mg of omalizumab every 4 weeks should be the third-line option for patients with CSU as it has demonstrated efficacy and safety and is approved for use in this setting with a maximum dose of 300-450- 600 mg every 4 weeks.
- Patient could be considered a nonresponder if he or she did not achieve disease control after 6 months of treatment with omalizumab.
- It is better to reduce the dose by 150 mg every 4 weeks.
- Patients with CU gained complete and rapid symptom relief after reinitiation of omalizumab and withdrawal of antihistamines and did not experience any relevant adverse effects.

Ciclosporin

- The European guidelines position ciclosporin as the fourth-line treatment for nonresponders to omalizumab.
- Ciclosporin has extensive adverse effects and can be used safely for up to 2 years. It is absolutely contraindicated in pregnancy and in patients with uncontrolled hypertension or abnormal kidney function.
- Ciclosporin is used at a dose of 2.5 to 5 mg/kg to treat CSU in omalizumab resistant patients. As routine tests, they mentioned differential blood count, biochemistry, and kidney and liver function tests.

Corticosteroids

- Guidelines recommend short-term tapering courses of corticosteroids to treat severe CU exacerbations, particularly in patients with concomitant angioedema due to the risk of secondary respiratory difficulty.
- A short course of oral corticosteroids can help reduce disease duration or activity in patients with acute urticaria or acute CSU exacerbations. A short, 10-day course of corticosteroids is used to treat exacerbations or acute episodes as well as applying a tapering schedule before switching to another treatment.

1.3.2 British Association of Dermatologists (BAD) Guidelines for the Management of People with Chronic Urticaria (2021)

The most recent British guidelines for the management of urticaria were published in the British Journal of Dermatology in 2021[10]. A summary of the recommendations can be found below:

First-line treatment options for people with chronic spontaneous urticaria (CSU)

- Offer a **second-generation H1-antihistamine**, using a regular daily licensed dose (strong).
- Do not offer first-generation H1-antihistamines routinely, unless there is no alternative, due to concerns about their short- and long-term effects on the central nervous system (strong against).
- Offer updosing (i.e. increasing the dose above the licensed dose) of a single second-generation H1- antihistamine, by up to fourfold the licensed dose, to people whose symptoms are inadequately controlled by the standard licensed dose, provided it is tolerated and there is no caution or contraindication (strong). Attempt stepwise dose reduction following complete symptom control. There is no evidence to guide the optimum duration of updosing or speed of dose reduction.
- Consider switching from one second-generation H1-antihistamine to another in people whose symptoms do not respond adequately to, or who do not tolerate, the first drug at standard or increased doses (good practice point).
- There is insufficient evidence to make a recommendation on using two different second-generation H1-antihistamines at the same time.
- Do not updose first-generation H1-antihistamines (strong against).
- Consider **montelukast**, in addition to a second-generation H1-antihistamine, in people whose symptoms are inadequately controlled by standard and increased doses of second-generation H1-antihistamines (weak).
- There is insufficient evidence to recommend routine addition of H2-antihistamines to second-generation H1-antihistamines for people whose symptoms are inadequately controlled by the latter. However, they may be considered if urticaria is associated with dyspepsia, although dyspepsia should be investigated appropriately.
- Consider oral prednisolone (e.g. 0.5 mg kg^{-1}) for short, infrequent courses of a few days as rescue treatment to control severe exacerbations, in addition to continued use of a second-generation H1-antihistamine (weak).

- Do not offer long-term systemic corticosteroids unless there is no other option. Use the lowest effective dose for the shortest possible period (strong against).

Second-line treatment options for people with chronic spontaneous urticaria

For people with CSU with an inadequate response to first-line treatment, the following additional investigations may be relevant when considering the next treatment options.

- Do not offer autologous serum skin tests (ASSTs) or autologous plasma skin tests (APSTs) routinely (strong against).
- Consider measuring total IgE levels: a high total IgE level may indicate a higher probability of early disease responsiveness to omalizumab, whereas a normal total IgE level may indicate disease responsiveness to ciclosporin (weak).
- If available, consider a basophil histamine release assay (BHRA), although it is not yet subject to a national quality assurance scheme. A positive BHRA may indicate a higher probability of disease responsiveness to ciclosporin and slower or delayed response to omalizumab, whereas a negative BHRA may indicate a higher probability of disease responsiveness to omalizumab. Note: total IgE levels and BHRAs are only indicative and may not reflect actual clinical responsiveness in all patients (weak).
- Offer **omalizumab**, in addition to a second generation H1-antihistamine, to people whose symptoms are inadequately controlled by first-line options (strong).
- Offer **ciclosporin** for 3–6 months, in addition to a second-generation H1-antihistamine, to people whose symptoms are inadequately controlled by first-line options (strong).
- Avoid long-term use of ciclosporin where possible; if not, use at the lowest effective dose, interrupt treatment periodically to confirm continued requirement, and consider alternative agents (strong).

1.4 International Guidelines

1.4.1 Taiwanese Dermatological Association Consensus for the Definition, Classification, Diagnosis, and Management of Urticaria (2021)

The following guideline does not provide a specified grade of evidence or level of recommendation[11].

Classification of urticaria according to its frequency, duration, and causes:

- A given case of urticaria can be classified as acute or chronic based on its duration, with acute urticaria defined as the spontaneous occurrence of wheals, angioedema, or both for 6 weeks, while CU is defined as the sudden occurrence of wheals and/or angioedema for >6 weeks. Fig. 1 presents an algorithm for the clinical classification of the acute and chronic forms, as well as for the various CU subtypes, and includes footnotes providing additional information regarding causes and alternative names for several subtypes.

Diagnosis

- The diagnosis of urticaria is primarily based on the symptoms and signs of the disease. The difference between acute and chronic urticaria is based on the duration of occurrence of wheals and/or angioedema. The presence of the disease for more than six weeks is defined as chronic urticaria.
- In recent years, substantial progress has been achieved in identifying the causes of the different types and subtypes of urticaria.

Patient history

Without necessarily aiming to identify all the potential causative factors, the first step in making an accurate diagnosis is taking a thorough patient history, especially for those patients with a disease duration of more than 6 weeks. Patients should be questioned regarding all the following points:

a. Characteristics:
    i. time of onset of disease;
    ii. frequency/duration;
    iii. diurnal variation;
    iv. occurrence in relation to weekends, holidays, seasons, and foreign travels;
    v. shape, size, and distribution of wheals;
    vi. associated angioedema;
    vii. associated subjective symptoms of lesions, e.g., itch and pain
b. History:
    i. family and personal history regarding urticaria and atopy;
    ii. previous or current allergies, infections, internal diseases, or other possible causes;
    iii. psychosomatic and psychiatric diseases;

iv. relationship to the menstrual cycle;
v. smoking habits (especially, the use of perfumed tobacco products);
vi. type of work;
vii. hobbies;
viii. stress (eustress and distress);
ix. previous therapy and response to therapy
x. previous diagnostic procedures/results;
xi. history of anhidrosis or hypohidrosis

c. Quality of life:

- Assess the quality of life related to urticaria and emotional impact using evaluation tools, such as the chronic urticaria quality of life questionnaire (CU-Q2oL).
- The second step of the diagnosis is a physical examination of the patient. When indicated by the patient history, this should include diagnostic provocation tests including drug, food, and physical tests. Intensive and costly general screening programs for causes of urticaria are not recommended for most cases.
- **Table 4** specifies the recommended diagnostic tests for frequent urticaria subtypes. Briefly, for patients with CSU, the recommended routine diagnostic tests include differential blood counts, D-dimer, and ESR or CRP. The extended diagnostic tests are recommended only when these factors are suspected based on the patients' history. For example, for patients with CSU, functional autoantibodies may include anti-thyroid autoantibodies, anti-nuclear antibodies (ANA), anti-FcεRI or anti-IgE antibodies, and so on

Table 4. Recommended Diagnostic Tests in Frequent Urticaria Subtypes. Retrieved from the Taiwanese Dermatological Association 2021 Guideline.

Types	Subtypes	Routine diagnostic tests (recommended)	Extended diagnostic program[b] (suggested based on history only) to identify eliciting factors & rule out possible differential diagnoses if indicated
Spontaneous urticaria	Acute spontaneous urticaria	None	None[c]
	Chronic spontaneous urticaria	Differential blood count & ESR or CRP Omission of suspected drugs (e.g., NSAIDs) D-dimer	(1) Thyroid hormones & autoantibodies (2) Autologous serum skin test or basophil activation test (3) Type I allergy (IgE, MAST, CAP) (4) Functional autoantibodies (ANA, etc.) (5) Infectious diseases (e.g., *Helicobacter pylori*) (6) Lesional skin biopsy (7) Skin tests including physical tests (8) Tryptase[d] (9) Pseudoallergen-free diet for 3 weeks
Inducible urticaria	Cold urticaria	Cold provocation & threshold test (ice cube, cold water, cold wind)	Differential blood count & ESR/CRP cryoproteins rule out other diseases, especially infections
	Delayed pressure urticaria	Pressure test	None
	Heat urticaria	Heat provocation & threshold test	None
	Solar urticaria	UV & visible light of different wavelengths & threshold test	Other light-induced dermatoses ruled out
	Symptomatic Dermographism	Elicit dermographism & threshold test (dermographometer)	Differential blood count, ESR/CRP
	Vibratory angioedema	Test with vortex	None
	Aquagenic urticaria	Wet cloths at body temperature applied for 20 min	None
	Cholinergic urticaria	Exercise & hot bath provocation	None
	Contact urticaria	Cutaneous provocation test. Skin tests with immediate readings, e.g., prick test, prick-by-prick test, patch test	None

Clinical management of chronic urticaria

Treatment goal

- Whether the treatment goal should be complete relief from all symptoms or whether a UAS7 score of ≤ 5 could be deemed sufficient as the goal of treatment. After discussion, it was ultimately decided that a UAS7 score of ≤ 5 should be the treatment goal and that the UAS score or response to a medication can be used to determine whether the given treatment is effective.

- **Fig. 4** shows the recommended treatment algorithm for CSU, including tracks for both non-drug and pharmacologic therapies. For CSU, continuous modern **second-generation antihistamines** (sgAHs) should be taken regularly rather than as-needed to reduce disease flares and improve the quality of life.

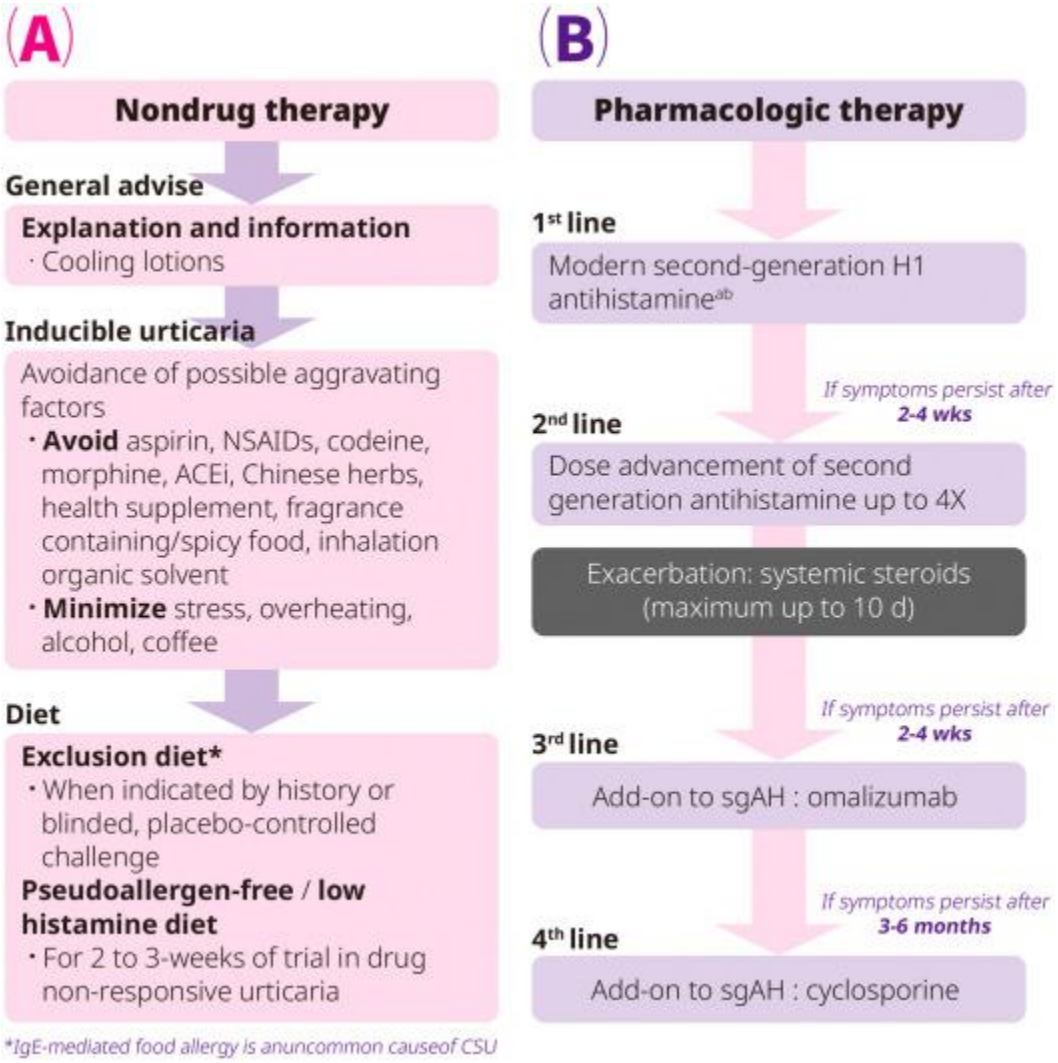


Figure 4. *Recommended treatment algorithm included (A) Nondrug therapy (B) Pharmacologic therapy for chronic spontaneous urticaria.*

- The recommended dosages of the first-line use of these sgAHs are listed as follow: cetirizine (10 mg/day), desloratadine (5 mg/day), fexofenadine (180 mg/day) and levocetirizine (5 mg/day). The benefit of up-dosing modern sgAHs have been verified for multiple drugs, including cetirizine, desloratadine, fexofenadine and levocetirizine.

- For those patients do not respond well to antihistamines, omalizumab and cyclosporine are listed as the third-line and the forth-line treatments, respectively

Clinical management of acute urticaria

- Acute urticaria differs from CU by spanning no more than 6 weeks. The diagnosis of urticaria or angioedema is made when episodes are largely limited to the skin (including mucosal tissue) but are not associated with major systemic symptoms. It is important to ask and educate the patients on symptoms of anaphylaxis, which is different from urticaria/angioedema and might be life-threatening, including wheezing/cough, vomiting/diarrhea, dizziness/consciousness disturbance, or hypotension/heart rate variations. There are several potential causes of acute urticaria, including food allergy, drug reactions (ex. NSAIDs, ACE inhibitors, and opiates), insect bite reactions, infections (ex. EBV infections or parvovirus B19), idiopathic causes, or physical urticaria.
- Treatment of acute urticaria includes the avoidance and removal of those potential factors.
- After eliminating these potential triggers, antihistamines are the first-line therapy for persistent symptoms.
- In severe cases, **oral corticosteroids** might be necessary to treat acute urticaria and angioedema. A trial of a short course of oral corticosteroids can be also considered if symptoms are severe or not resolving with the administration of antihistamines. However, the benefit of oral corticosteroids for acute urticaria is insufficient to warrant routine use of oral corticosteroids rather than antihistamines.
- **Epinephrine** should be used as the third-line treatment (after H1 and H2 antihistamines and systemic steroids) for severe angioedema. Notably, it should be the first-line treatment if the patient presents with serious respiratory, cardiac, or gastrointestinal symptoms. If the diagnosis of anaphylaxis has not been excluded, epinephrine should also be administered.
- The resulting treatment algorithm is shown in **Fig. 5** and includes specific information on when to administer epinephrine, systemic steroids, and H1 and H2 antihistamines.

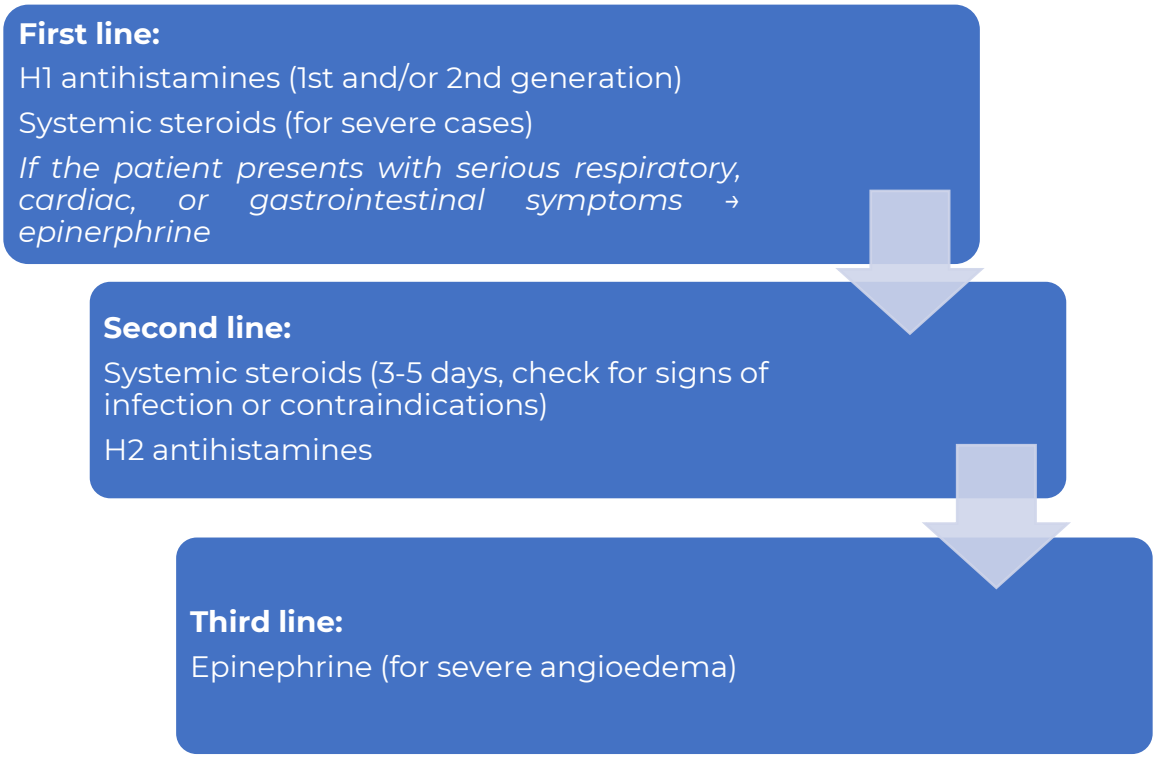


Figure 5. *Recommended treatment algorithm for acute urticaria.*

Management in special populations

Elderly patients

- The main characteristics of geriatric CSU patients are fewer wheals, lower rates of angioedema, less frequent dermographism, a lower frequency of autologous serum skin test positivity, and equal sex distribution. Comorbidities, polypharmacy, and organ insufficiency in the elderly make the treatment of geriatric urticaria very difficult.
- Thoroughly reviewing and adjusting their medications (including ACEIs, Aspirin, and other NSAIDs), avoiding eliciting factors, managing comorbidities, checking renal and liver functions, and surveying possible underlying diseases (diabetes, dysthyroidism, autoimmune diseases, and malignancies) are keys to successful treatment.
- In general, drug and dose selection for elderly patients should be considered carefully due to possible drug interactions or adverse effects, such as urinary retention, dry mouth, glaucoma, and central nervous system effects, which are most commonly seen among first generation H1 antihistamines. In addition, the risk of falls or traffic accidents in patients should be taken into consideration when prescribing antihistamines.

- Equally, the use of medications for CSU in elderly patients may be considered when the potential benefits outweigh the potential risks to the patient. In elderly patients with multiple comorbidities or impaired renal/liver functions, omalizumab may be taken into consideration due to his safety and effectiveness.

Patients with renal or hepatic impairment

- Dose adjustment may be needed for patients with impaired renal or hepatic function. Dose adjustment should also be considered for patients receiving dialysis (whether hemodialysis or peritoneal dialysis).
- The use of first-generation H1-antihistamines should be avoided in patients with severe liver or renal disease because of their inappropriate sedating effect. Non-sedating sgAHs are suggested to be used with caution in patients with severe liver and renal diseases.
- The quality of evidence supporting the use of phototherapy in histamine-refractory CU is low. However, narrow-band UVB phototherapy is a well-tolerated treatment modality and can be used safely in subjects with systemic diseases such as renal and liver diseases, as well as in pregnant women and children.

Pediatric patients

- For children under the age of 12 years, first generation H1-antihistamines are no longer recommended due to more adverse effects.
- Non-sedating sgAHs at the suggested dose are recommended as first-line treatment for patients under the age of 12 years.
- SgAHs administered up to fourfold the standard appears to be safe even in children with CSU, but only cross-section studies show its efficacy and tolerability. We recommend using a fourfold licensed dosage if symptoms persist for 2-4 weeks after first-line treatment.
- Omalizumab (for children over 12 years of age) and cyclosporine are recommended as third-line and fourth-line treatments according to the adult treatment algorithm.
- A multicenter retrospective case series showed a favorable response to standard-dose omalizumab therapy at rates similar to adults. As a result, we recommended omalizumab in pediatric patients with recalcitrant CSU older than 6 years after second-line treatment fails.

Pregnant women

- In principle, the same considerations should apply to the treatment of pregnant women. As a rule, considering the potential risks and benefits,

prescribing clinicians should avoid the use of any systemic treatment in pregnant women, especially during the first trimester. At the same time, pregnant women also have a right to receive the best therapy possible. The general consideration about treatment of CSU for pregnant women is similar to that of the general population, but attention should be paid to some details. Some of the modern sgAHs are now available for purchase without a prescription and have, thus, been used widely in treating both allergic rhinitis and urticaria. It can be assumed that many pregnant women have used these drugs, especially during the earliest stages of pregnancy (i.e., before they were aware that they were pregnant).

- H1 antihistamines in the first trimester illustrate no increased overall risk of major malformations or other adverse pregnancy related outcomes (spontaneous abortions, prematurity, stillbirths, and low birth weight).
- Glucocorticoids may be used cautiously during pregnancy for a short duration for acute urticaria or exacerbation of CSU if clinically appropriate. Betamethasone and dexamethasone cross the placenta with similar maternal and fetal concentrations. Non-fluorinated corticosteroids (prednisone, methylprednisolone, and hydrocortisone) are largely metabolized by placental 11b-hydroxysteroid dehydrogenase, thus, minimal amounts reach the fetal circulation.
- Therefore, glucocorticoids for prolonged use should be limited to 7.5 mg/day and not more than 20 mg/day. Most of the data on cyclosporine comes from transplant recipients, who are generally given higher doses (8-10 mg/ kg/day) than dermatologic patients.
- Cyclosporine is not an animal or human teratogen. Cohorts have been followed through early childhood, with no detectable long-term neurodevelopmental, nephrotoxic, or immunologic effects in children. However, cyclosporine can cause maternal hypertension and should be reserved as rescue therapy for severe disease.

Breastfeeding women

- If used by a nursing mother, low concentrations of all H1 antihistamines will be excreted from the mother's breast milk. Furthermore, nursing infants have been known to occasionally become sedated after ingesting first generation H1 antihistamines transferred from breast milk. For this reason, first-generation antihistamines should be used with caution, and parents should be counseled to monitor children for signs of irritability or drowsiness.
- Nonsedating sgAHs are preferred.

- Non fluorinated corticosteroids are compatible with breastfeeding since they are minimally excreted in breast milk (5-25%).
- As for omalizumab, breastfeeding was allowed because the omalizumab antibody-based structure is expected to be destroyed after oral ingestion.

1.4.2 International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis, and Management of Urticaria (2021)

This guideline was published as a joint initiative of the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA²LEN) and its Urticaria and Angioedema Centers of Reference and Excellence (UCAREs and ACAREs), the European Dermatology Forum (EDF; EuroGuiDerm), and the Asia Pacific Association of Allergy, Asthma and Clinical Immunology. was developed following the methods recommended by Cochrane and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group[12].

The targets and aims of pharmacological therapies and the need for continued treatment

Current recommended treatment options for urticaria aim to target mast cell mediators such as histamine, or activators, such as autoantibodies. Novel treatments currently under development aim to silence mast cells via inhibitory receptors or to reduce mast cell numbers. The overall goal of all of these symptomatic treatments is to help patients to be free of signs and symptoms until their urticaria shows spontaneous remission. To achieve this, pharmacological treatment should be continuous, until no longer needed. Non-sedating 2nd generation H1-antihistamines, for example, should be used daily, to prevent the occurrence of wheals and angioedema, rather than on demand.

I. H1-antihistamine treatment

- H1-antihistamines have been available for the treatment of urticaria since the 1950s. The older 1st generation H1-antihistamines have pronounced anticholinergic and sedative effects, and many interactions with alcohol and other drugs, such as analgesics, hypnotics, sedatives, and mood-elevating drugs, have been described. It is strongly recommended not to use 1st generation H1-antihistamines any longer in allergy both for adults and especially in children. Based on strong evidence regarding potentially serious side effects of 1st generation H1-antihistamines (lethal overdoses have been reported), we recommend against their use for the routine management of CU as first-line agents.

- Modern 2nd generation H1-antihistamines are minimally or non-sedating and free of anticholinergic effects. Most but not all 2nd generation H1-antihistamines have been tested specifically in urticaria, and evidence supports the use of cetirizine, desloratadine, fexofenadine, levocetirizine and loratadine. We recommend the use of a standard dosed modern 2nd generation H1-antihistamines as the first-line symptomatic treatment for urticaria. However, no recommendation can be made on which to choose because, to date, well-designed clinical trials comparing the efficacy and safety of all modern 2nd generation H1- antihistamines in urticaria are largely lacking.
- Some patients with urticaria, who show insufficient response to a standard-dosed 2nd generation H1-antihistamine, benefit from updosing which is preferred over mixing different 2nd generation H1-antihistamines as their pharmacologic properties are different. We, therefore, recommend to increase the dose up to fourfold, in such patients. Patients need to be informed that 2nd generation H1-antihistamine updosing is off-label and higher than fourfold is not recommended as it has not been tested. However, updosing has been suggested in the guidelines for urticaria since the year 2000 and so far no serious adverse events have been reported, nor has a side effect ever been reported in the literature attributed to long-term intake and potential accumulation.

II. Omalizumab treatment

- Omalizumab is the only other licensed treatment in urticaria for patients who do not show sufficient benefit from treatment with a 2nd generation H1-antihistamine, and therefore the next step in the algorithm. Omalizumab (anti-IgE) has been shown to be very effective and safe in the treatment of Chronic spontaneous urticaria (CSU). Omalizumab has also been reported to be effective in cholinergic urticaria, cold urticaria, solar urticaria, heat urticaria, symptomatic dermographism, and delayed pressure urticaria.
- In CSU, omalizumab prevents wheal and angioedema development, markedly improves quality of life, is suitable for long-term treatment, and effectively treats relapse after discontinuation.
- The recommended initial dose in CSU is 300 mg every 4 weeks. Dosing is independent of total serum IgE. Patients with urticaria who do not show sufficient benefit from treatment with omalizumab at the licensed dose of 300 mg every 4 weeks can be treated with omalizumab at higher doses, shorter intervals, or both.

- Studies support the use of omalizumab treatment at doses up to 600 mg and intervals of 2 weeks, in patients with insufficient response to standard-dosed omalizumab.

III. Ciclosporin treatment

- Patients with urticaria who do not show sufficient benefit from treatment with omalizumab, should be treated with ciclosporin 3.5–5 mg/ kg per day. Ciclosporin is immunosuppressive and has a moderate, direct effect on mast cell mediator release. Efficacy of ciclosporin in combination with a modern 2nd generation H1-antihistamine has been shown in placebo-controlled trials as well as open controlled trials in CSU, but this drug cannot be recommended as standard treatment due to a higher incidence of adverse effects.
- Ciclosporin is off-label for urticaria and is recommended only for patients with severe disease refractory to any dose of antihistamine and omalizumab in combination. However, ciclosporin has a far better risk/benefit ratio compared with long-term use of steroids.

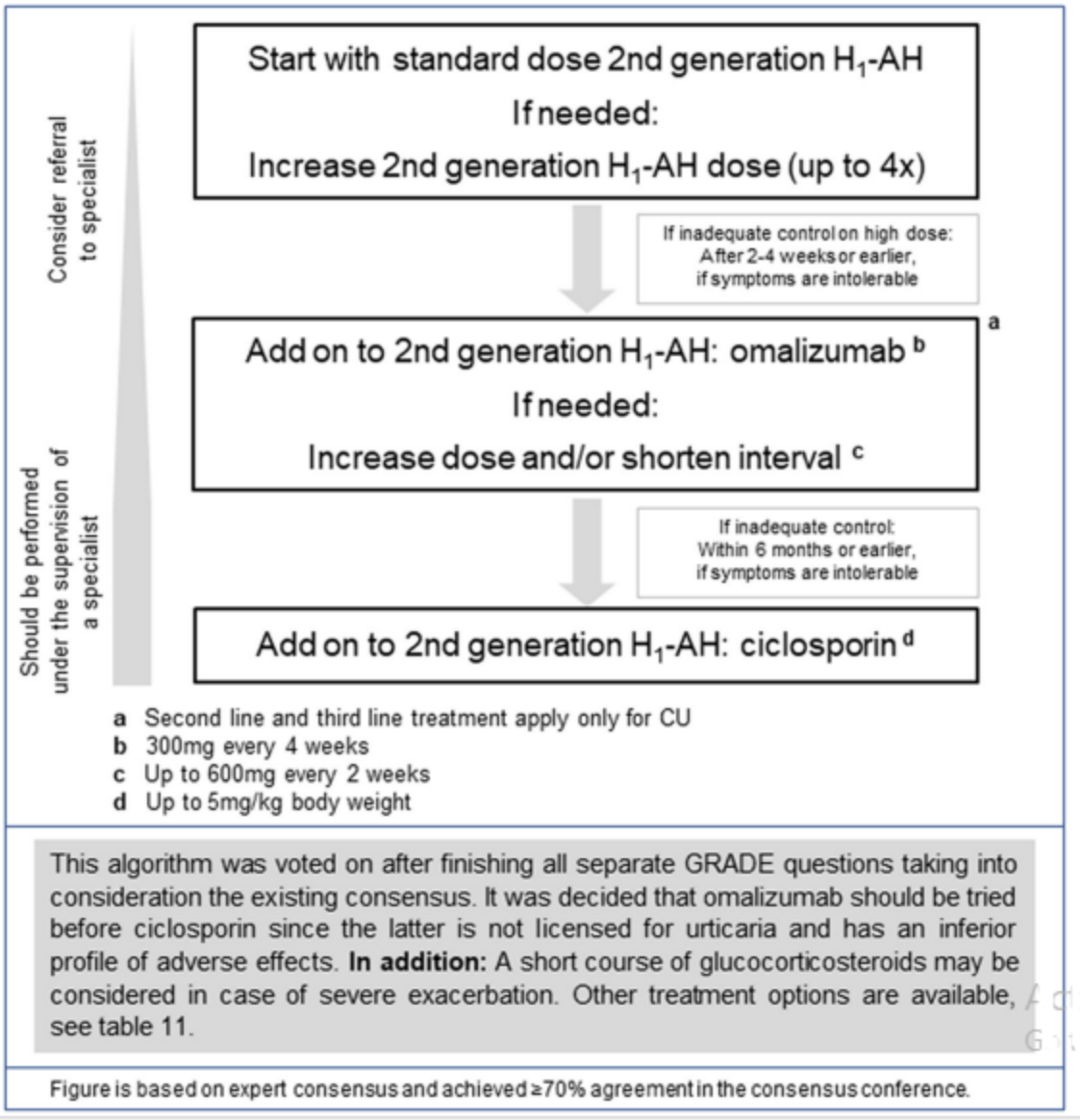


***Figure 6**. Recommended treatment algorithm for urticaria. Retrieved from the EAACI/GA²LEN/EuroGuiDerm/APAAACI guidelines (2021)*

Treatment of special populations

I. Children

- Many clinicians use 1st generation H1-antihistamines as their first-choice treatment of children with urticaria assuming that their safety profile is better known than that of the modern 2nd generation H1- antihistamines due to a longer experience with them. Also, the use of modern 2nd generation H1-antihistamines is not licensed for use in children less than 6 months of age in many countries. However, 1st generation H1-antihistamines have an inferior

safety profile compared with 2nd generation H1-antihistamines, and are, therefore, not recommended as first-line treatment in children with urticaria.

- 2nd generation H1-antihistamines with proven efficacy and safety in the pediatric population include cetirizine, desloratadine, fexofenadine, levocetirizine and loratadine.
- The choice of which 2nd generation H1-antihistamines to use in children with urticaria should take into consideration the age and availability as not all are available as syrup or fast dissolving tablet suitable for children. The lowest licensed age also differs from country to country. All further steps should be based on individual considerations and be taken carefully as updosing of antihistamines, and further treatment options are not well studied in children.

II. Pregnant and lactating women

- The same considerations in principle apply to pregnant and lactating women.
- Regarding treatment, no reports of birth defects in women having used modern 2nd generation H1-antihistamines during pregnancy have been reported to date. However, only small sample size studies are available for cetirizine and one large meta-analysis for loratadine. Furthermore, as several modern 2nd generation H1-antihistamines are now prescription free and used widely in both allergic rhinitis and urticaria, it must be assumed that many women have used these drugs especially in the beginning of pregnancy, at least before the pregnancy was confirmed.
- Nevertheless, since the highest safety is mandatory in pregnancy, the suggestion for the use of modern 2nd generation H1-antihistamines is to prefer loratadine with the possible extrapolation to desloratadine and cetirizine with a possible extrapolation to levocetirizine. All H1-antihistamines are excreted in breast milk in low concentrations.
- Use of 2nd generation H1-antihistamines is advised, as nursing infants occasionally develop sedation from the old 1st generation H1-antihistamines transmitted in breast milk.
- The increased dosage of modern 2nd generation H1- antihistamines can only be carefully suggested in pregnancy since safety studies have not been done, and with loratadine, it must be remembered that this drug is metabolized in the liver which is not the case for its metabolite desloratadine.
- 1st generation H1-antihistamines should be avoided.
- The use of omalizumab in pregnancy has been reported to be safe, and to date, there is no indication of teratogenicity.

- All further steps should be based on individual considerations, with a preference for medications that have a satisfactory risk-to-benefit ratio in pregnant women and neonates with regard to teratogenicity and embryotoxicity. For example, ciclosporin, although not teratogenic, is embryo-toxic in animal models and is associated with preterm delivery and low birth weight in human infants. Whether the benefits of ciclosporin in CU are worth, the risks in pregnant women will have to be determined on a case-by-case basis. However, all decisions should be re-evaluated according to the current recommendations published by regulatory authorities.

1.5 Systematic Reviews & Meta Analyses

The table below tackles a systematic review and meta-analyses issued in **2022** for Urticaria.

Table 5. Systematic Review and Meta-Analysis for Urticaria

Study	Author (year)	Study Title	Primary Objective	Outcomes	Results
1	Wang Bei et al.[13] (2023)	**"Comparing four immunosuppressive agents for chronic spontaneous urticaria-A network meta-analysis"**	To compare the efficacy, safety, and incidence of adverse effects of four immunosuppressive medicines (tripterygium glycosides, methotrexate, cyclosporine A, and azathioprine) in combination with antihistamines in treating CSU.	The primary outcome measures being Urticaria Activity Score 7 (UAS7) and adverse effects. - Summarize all available evidence and compare treatments that evaluated the efficacy and safety profiles of pharmacological treatments in CSU patients refractory to treatment with immunosuppressive agents.	• This study pooled data from seven randomized clinical trials with 410 participants. The standardized mean differences for change in UAS7 were 0.10 (95% confidence interval (CI), 0.01 to 0.68) for cyclosporine A plus antihistamine; 0.03 (95% CI, 0.00 to 0.23) for azathioprine plus antihistamine; 0.52 (95% CI, 0.32 to 0.85) for tripterygium glycosides plus antihistamine; and 1.54 (95% CI, 0.64 to 3.67) for methotrexate plus antihistamine. • There were no significant differences in side effects between these medicines in the limited number of trials and clinical samples.

2	Hong-yu Fu et al.[14] (2023)	**"Effect and safety of probiotics for treating urticaria: A systematic review and meta-analysis"**	To assess the effect and safety of probiotics for treating urticaria.	To evaluate the efficacy and safety of probiotic treatment of urticaria and provide evidence-based medical evidence for clinical application.	• The therapeutic effect of the probiotic group was significantly higher than the control group (placebo or antihistamines) (RR = 1.09, 95% CI: 1.03–1.16, p= 0.006). And compared with the placebo group, the therapeutic effect of single probiotic group was significantly improved (RR = 1.11, 95% CI: 1.01– 1.21, p= 0.03). • Regarding therapeutic effect, there was no statistically significant difference between the multiple probiotics group and placebo group (RR = 1.00, 95% CI: 0.94 ~ 1.07, p= 0.91); the therapeutic effect of single probiotic combined antihistamine group was significantly higher than the antihistamine group (RR = 1.13, 95% CI: 1.07–1.19, p).

3	Chaichan et al.[15] (2023)	**"Comparative Safety Profiles of Individual Second-Generation H1-Antihistamines for the Treatment of Chronic Urticaria: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials"**	To compare the safety profiles of individual sgAHs and/or dosing regimens in adolescents or adult patients with CU using a systematic review and network meta-analysis of all available evidence.	Relevant safety outcomes included treatment unacceptability (all-cause discontinuation), tolerability (discontinuation due to any adverse events), adverse events, serious adverse events, central nervous system (CNS) side effects, and anticholinergic side effects.	• There were no statistically significant differences between the results of sgAH treatment for serious adverse events and those for anticholinergic side effects. • On the basis of the ranking of safety profiles, emedastine 4 mg, mizolastine 10 mg, and cetirizine 10 mg were the top 3 ranked treatments with unfavorable safety profiles associated with CNS side effects and any adverse events.

Section 2.0 Drug Therapy

2.1 Second-Generation H1 Antihistamines

2.1.1 Desloratadine

Information on desloratadine is detailed in the table below:[16,17]

Table 6. Desloratadine Drug Information

SCIENTIFIC NAME DESLORATADINE	
SFDA Classification	OTC
Trade Name(s) on Saudi Market	DESLIN, RINA, LORETA, DESTAMIN, AERIALLERG, AERIUS, DESLOR
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L50
Drug Class	ANTIHISTAMINES
Drug Sub-class	SECOND-GENERATION H1 RECEPTOR ANTAGONIST
ATC Code	R06AX27
Pharmacological Class (ASHP)	ANTIHISTAMINES, 2ND GENERATION
DRUG INFORMATION	
Dosage Form	Oral solution Syrup Film-coated tablet
Route of Administration	Oral Use
Dose (Adult) [DDD]*	**New onset: Oral:** Initial: 5 mg once daily. If symptom control is inadequate, may immediately increase to 5 mg twice daily. **Chronic spontaneous: Oral:** Initial: 5 mg once daily. If symptom control is inadequate, may increase in 5 mg/day

	increments every 1 to 4 weeks up to 10 mg twice daily; periodically reevaluate necessity for continued treatment.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Infants 6 to ≤11 months: 1 mg once daily. Children ≤5 years: 1.25 mg once daily. Children 6 to ≤11 years: 2.5 mg once daily. Children ≥12 years and Adolescents: 5 mg once daily.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	AGE
AGE (Age Edit)	For use in infants 6 months of age and above
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** diarrhea, irritability, fever, headache. **Most serious**: Upper respiratory tract infections, urinary tract infection.
Drug Interactions*	**Category X:** Azelastine, Bromperidol, Flunarizine, Kratom, Olopatadine, Orphenadrine, Oxomemazine, Paraldehyde, Pitolisant, Thalidomide.

Special Population	**Slow metabolizers:** Use with caution in patients known to be slow metabolizers of desloratadine (incidence of side effects may be increased).
Pregnancy	Guidelines for the use of antihistamines in the treatment of allergic rhinitis or urticaria in pregnancy are generally the same as in nonpregnant females. Second generation antihistamines may be used for the treatment of allergic rhinitis and urticaria during pregnancy; however, information related to the use of desloratadine in pregnancy is limited and other medications may be preferred.
Lactation	According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should consider the risk of exposure to the infant and the benefits of treatment to the mother. When treatment with an antihistamine is needed in breastfeeding women, second generation antihistamines are recommended; however, agents other than desloratadine may be preferred.
Contraindications	Hypersensitivity to desloratadine, loratadine, or any component of the formulation.
Monitoring Requirements	N/A
Precautions	***Concerns related to adverse effects:*** **-Hypersensitivity:** Hypersensitivity reactions (including anaphylaxis) have been reported with use; discontinue therapy immediately with signs/symptoms of hypersensitivity. ***Disease-related concerns:*** **-Hepatic impairment:** Use with caution in patients with severe hepatic impairment.

	-Renal impairment: Use with caution in patients with severe renal impairment. ***Concurrent drug therapy issues:*** **-Sedatives:** Effects may be potentiated when used with other sedative drugs or ethanol. ***Dosage form specific issues:*** **-Phenylalanine:** Some products may contain phenylalanine.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

HTA reviews and recommendations of urticaria treatment options are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

CONCLUSION STATEMENT – DESLORATADINE

Desloratadine is recommended as a first-line treatment of urticaria. It is given as 5 mg once daily for adults and can be increased to 5mg twice daily. It can be given for infants ≥ 6 months.

2.1.2 Loratadine

Information on loratadine is detailed in the table below:[18,19]

Table 7. Loratadine Drug Information

SCIENTIFIC NAME LORATADINE	
SFDA Classification	OTC
Trade Name(s) on Saudi Market	RESTAMINE, LORA, CLARINASE
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L50

Drug Class	ANTIHISTAMINES
Drug Sub-class	SECOND-GENERATION H1 RECEPTOR ANTAGONIST
ATC Code	R06AX13
Pharmacological Class (ASHP)	ANTIHISTAMINES, 2ND GENERATION
DRUG INFORMATION	
Dosage Form	Syrup Tablets
Route of Administration	Oral Use
Dose (Adult) [DDD]*	**New onset: Oral:** Initial: 10 mg once daily. If symptom control is inadequate, may immediately increase to 10 mg twice daily. **Chronic spontaneous: Oral:** Initial: 10 mg once daily. If symptom control is inadequate after 1 to 4 weeks, may increase to 10 mg twice daily. Although current guidelines state that antihistamine doses may be increased up to 4 times the standard dose (eg, to 20 mg twice daily), there is limited evidence for greater efficacy with this dose of loratadine, and other antihistamines are preferred. Periodically reevaluate necessity for continued treatment.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	Limited data available. Considered first-line therapy for management of chronic urticaria; if response inadequate after 2 to 4 weeks of therapy or symptoms intolerable, consider increasing the dose of loratadine (as age and weight permits) as second-line treatment rather than changing therapy. Children ≥2 to <6 years: 5 mg once daily. Children ≥6 years and Adolescents: 10 mg once daily.

Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** - CrCl ≥30 mL/minute: No dosage adjustment necessary (Matzke 1990; manufacturer's labeling). - CrCl <30 mL/minute: 10 mg every 48 hours. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	AGE
AGE (Age Edit)	For use in children 2 years of age and older
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** headache. **Most serious**: palpitation, tachycardia, syncope, urinary tract infection.
Drug Interactions*	**Category X:** Aclidinium, Azelastine, Bromperidol, Cimetropium, Eluxadoline, Flunarizine, Glycopyrrolate, Glycopyrronium, Ipratropium, Kratom, Levosulpiride, Olopatadine, Orphenadrine, Oxatomide, Oxomemazine, Paraldehyde, Pitolisant, Potassium Chloride, Potassium Citrate, Pramlintide, Revefenacin, Thalidomide, Tiotropium, Umeclidinium.
Special Population	N/A
Pregnancy	Guidelines for the use of antihistamines in the treatment of allergic rhinitis or

	urticaria in pregnancy are generally the same as in nonpregnant females. Loratadine may be used when a second-generation antihistamine is needed. The lowest effective dose should be used.
Lactation	Loratadine and its active metabolite, desloratadine, are present in breast milk. The relative infant dose (RID) of loratadine plus desloratadine has been calculated to be 1.1% when compared to a maternal dose of 40 mg/day of loratadine. Breastfeeding is considered acceptable when the RID is <10%. The estimated daily infant dose of loratadine equivalents via breast milk was calculated to be 29.1 mcg/day in a theoretical 4 kg infant. The half-life of loratadine in breast milk was reported to be 10.7 hours in one woman. Drowsiness and irritability have been reported in breastfed infants exposed to antihistamines. In general, second-generation antihistamines (e.g., loratadine) are less sedating as compared to their first-generation counterparts. If a breastfed infant is exposed to a second-generation antihistamine via breast milk, they should be monitored for irritability, jitteriness, or drowsiness. When treatment with an antihistamine is needed for the treatment of rhinitis and urticaria in breastfeeding women, a second-generation antihistamine, such as loratadine, is preferred. Antihistamines may decrease maternal serum prolactin concentrations when

	administered prior to the establishment of lactation.
Contraindications	Hypersensitivity to loratadine or any component of the formulation.
Monitoring Requirements	N/A
Precautions	**Disease-related concerns:** -Hepatic impairment: Hepatic impairment increases systemic exposure. Use with caution. -Renal impairment: Use with caution in patients with renal impairment. **Concurrent drug therapy issues:** **-**Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol**.** **Dosage form specific issues:** -Benzyl alcohol and derivatives: Some dosage forms may contain sodium benzoate/benzoic acid; benzoic acid (benzoate) is a metabolite of benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; the "gasping syndrome" consists of metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction (including convulsions, intracranial hemorrhage), hypotension, and cardiovascular collapse; some data suggests that benzoate displaces bilirubin from protein binding sites; avoid or use dosage forms containing benzyl alcohol derivative with caution in neonates. See manufacturer's labeling. -Phenylalanine: Some products may contain phenylalanine.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

HTA reviews and recommendations of urticaria treatment options are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

CONCLUSION STATEMENT – LORATADINE

Loratadine is recommended as a first-line treatment of urticaria. It is given as 10 mg once daily for adults and can be increased to 10mg twice daily. It can be given for children ≥ 2 years.

2.1.3 Fexofenadine

Information on fexofenadine is detailed in the table below:[20,21]

Table 8. Fexofenadine Drug Information

SCIENTIFIC NAME FEXOFENADINE	
SFDA Classification	OTC
Trade Name(s) on Saudi Market	FEXODINE, TELFAST, SARFEX, FEXOTEL, FENADEX, FEXOFIN
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L50
Drug Class	ANTIHISTAMINES
Drug Sub-class	SECOND-GENERATION H1 RECEPTOR ANTAGONIST, PIPERIDINE DERIVATIVE
ATC Code	R06AX26
Pharmacological Class (ASHP)	ANTIHISTAMINES, 2ND GENERATION
DRUG INFORMATION	
Dosage Form	Film-coated tablets Tablets
Route of Administration	Oral Use

Dose (Adult) [DDD]*	**New onset: Oral**: **Initial**: 180 mg once daily. If symptom control is inadequate, may immediately increase to 180 mg twice daily. **Chronic spontaneous**: Oral: 180 mg once daily. If symptom control is inadequate, add a different second-generation antihistamine; higher doses of fexofenadine have not been shown to be more effective in controlling urticaria symptoms in most patients.
Maximum Daily Dose Adults*	180 mg/day
Dose (pediatrics)	**Acute urticaria:** Limited data available: Children ≥6 to 11 years: Twice-daily formulations (eg, regular tablet): Oral: 30 mg every 12 hours. Children ≥12 years and Adolescents: Twice-daily formulations (eg, regular tablet): Oral: 60 mg every 12 hours. **Urticaria, chronic spontaneous:** Limited data available: **Note:** Considered first-line therapy for management of chronic urticaria; if response inadequate after 2 to 4 weeks of therapy or symptoms intolerable, consider increasing the dose of fexofenadine (as age and weight permits) as second-line treatment rather than changing therapy. Infants ≥6 months to Children <2 years: Twice-daily formulations (eg, oral suspension): Oral: 15 mg every 12 hours. Children ≥2 to <12 years: Twice-daily formulations (eg, oral suspension, orally-disintegrating tablet, regular tablet): Oral: 30 mg twice daily. Children ≥12 years and Adolescents: -Twice-daily formulations (eg, oral suspension, orally-disintegrating tablet,

	regular tablet): Oral: 60 mg every 12 hours. -Once-daily formulation: Oral: 180 mg once daily.
Maximum Daily Dose Pediatrics*	6 months to 2 years: 30mg/day 2 years to 11 years: 60mg/day 12 years and older: 180mg/day
Adjustment	Use of the once-daily formulation is not recommended in patients with eGFR <50 mL/minute/1.73 m^2 or on renal replacement therapies **Altered Kidney Function:** - eGFR ≥50 mL/minute/1.73 m^2: **Oral:** No dosage adjustment necessary. - eGFR 10 to <50 mL/minute/1.73 m^2: **Oral:** 60 mg every 12 to 24 hours. - eGFR <10 mL/minute/1.73 m^2: **Oral:** 60 mg every 24 hours.; monitor patients for signs and symptoms of drug accumulation and toxicity. **Augmented renal clearance (measured urinary CrCl ≥130 mL/minute/1.73 m^2):** - **Note:** Augmented renal clearance (ARC) is a condition that occurs in certain critically ill patients without organ dysfunction and with normal serum creatinine concentrations. Younger patients (<55 years of age) admitted post trauma or major surgery are at highest risk for ARC, as well as those with sepsis, burns, or hematologic malignancies. An 8- to 24-hour measured urinary CrCl is necessary to identify these patients. - **Oral:** No dosage adjustment necessary. **Hemodialysis, intermittent (thrice weekly):** Not dialyzable (manufacturer's labeling): - **Oral:** 60 mg every 24 hours.

	Peritoneal dialysis: Significant removal unlikely (large V_d): - **Oral:** 60 mg every 24 hours. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	AGE
AGE (Age Edit)	For use in infants 6 months of age and older
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** vomiting, headache. **Most serious**: fever, diarrhea, urinary tract infection, upper respiratory tract infection.
Drug Interactions*	**Category X:** Aclidinium, Azelastine, Bromperidol, Cimetropium, Eluxadoline, Flunarizine, Glycopyrrolate, Glycopyrronium, Ipratropium, Kratom, Levosulpiride, Olopatadine, Orphenadrine, Oxatomide, Oxomemazine, Paraldehyde, Pitolisant, Potassium Chloride, Potassium Citrate, Pramlintide, Revefenacin, Thalidomide, Tiotropium, Umeclidinium, .
Special Population	N/A
Pregnancy	Agents other than fexofenadine are preferred for the treatment of allergic conditions, such as rhinitis, pruritus, and urticaria, in pregnant women

Lactation	Fexofenadine is present in breast milk following administration of its parent compound, terfenadine, to breastfeeding mothers. Drowsiness and irritability have been reported in breastfed infants exposed to antihistamines; only irritability was reported in infants exposed to fexofenadine's parent compound, terfenadine. In general, second generation antihistamines are less sedating as compared to their first generation counterparts. If a breastfed infant is exposed to a second generation antihistamine via breast milk, they should be monitored for irritability, jitteriness, or drowsiness. When treatment with an antihistamine is needed in breastfeeding women, other second generation antihistamines with more information available regarding their use in this patient population are preferred.
Contraindications	When used for self-medication do not use if you ever had an allergic reaction to fexofenadine or any component of the formulation
Monitoring Requirements	N/A
Precautions	**Disease-related concerns:** - Renal impairment: Use with caution in patients with renal impairment; dosage adjustment may be recommended. **Dosage form specific issues:** - Orally disintegrating tablet: Some products may contain phenylalanine -Phenylalanine: Some products may contain phenylalanine.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

HTA reviews and recommendations of urticaria treatment options are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

CONCLUSION STATEMENT – Fexofenadine

Fexofenadine is recommended as a first-line treatment for urticaria. It is given as 180 mg/day for adults. It can be given to infants ≥ 6 months.

2.1.4 Cetirizine

Information on cetirizine is detailed in the table below:[22]

Table 9. Cetirizine Drug Information

SCIENTIFIC NAME **Cetirizine**	
SFDA Classification	OTC
Trade Name(s) on Saudi Market	CETRALON, FINALLERG
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L50
Drug Class	ANTIHISTAMINES
Drug Sub-class	SECOND-GENERATION H1 RECEPTOR ANTAGONIST, PIPERIDINE DERIVATIVE
ATC Code	R06AE07
Pharmacological Class (ASHP)	ANTIHISTAMINES, 2ND GENERATION
DRUG INFORMATION	
Dosage Form	Syrup Film-coated tablets Oral solution
Route of Administration	Oral Use
Dose (Adult) [DDD]*	**New onset:**

	Oral (off-label use): Initial: 10 mg once daily. If symptom control is inadequate, may immediately increase to 10 mg twice daily. **Chronic spontaneous:** **Oral:** Initial: 10 mg once daily. If symptom control is inadequate, may increase in increments of 10 mg/day every 1 to 4 weeks up to 20 mg twice daily. Periodically reevaluate necessity for continued treatment.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Urticaria, acute**: **Oral**: Limited data available: Infants ≥6 months and Children <2 years: 2.5 mg once daily. Children 2 to 5 years: 2.5 to 5 mg once daily. Children >5 years and Adolescents: 5 to 10 mg once daily. **Urticaria, chronic spontaneous**: Limited data available in Children >5 years and Adolescents. Note: Considered first-line therapy for management of chronic urticaria; if response inadequate after 2 to 4 weeks of therapy or symptoms intolerable, consider increasing the dose of cetirizine (as age and weight permits) as second-line treatment rather than changing therapy. Infants 6 to <12 months: 2.5 mg once daily. Infants ≥12 months and Children <2 years: Initial: 2.5 mg once daily; dosage may be increased to 2.5 mg twice daily. Children 2 to 5 years: Initial: 2.5 mg once daily; dosage may be increased

	to 2.5 mg twice daily or 5 mg once daily; maximum daily dose: 5 mg/day. Children 6 to 11 years: 5 mg once daily or twice daily. Children ≥12 years and Adolescents: 10 mg once daily.
Maximum Daily Dose Pediatrics*	10mg/day
Adjustment	**Altered Kidney Function:** - CrCl >31 mL/minute: No dosage adjustment necessary. - CrCl 11 to ≤31 mL/minute: 5 mg once daily. - CrCl ≤10 mL/minute: 5 mg once every 48 hours; may increase to 5 mg once daily based on tolerability and response for short-term use only (drug may accumulate with prolonged use at this dose). **Hepatic Impairment:** Mild to severe impairment: 5 mg once daily.
Prescribing edits*	AGE
AGE (Age Edit)	For use in infants 6 months of age and older
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** headache, somnolence. **Most serious**: palpitation, tachycardia, heart failure, syncope, urinary tract infection.
Drug Interactions*	**Category X:**

	Aclidinium, Azelastine, Bromperidol, Cimetropium, Eluxadoline, Flunarizine, Glycopyrrolate, Glycopyrronium, Ipratropium, Kratom, Levosulpiride, Olopatadine, Orphenadrine, Oxatomide, Oxomemazine, Paraldehyde, Pitolisant, Potassium Chloride, Potassium Citrate, Pramlintide, Revefenacin, Thalidomide, Tiotropium, Umeclidinium.
Special Population	Older adult: Use with caution in elderly patients; may be more sensitive to adverse effects.
Pregnancy	Guidelines for the use of antihistamines in the treatment of allergic rhinitis or urticaria in pregnancy are generally the same as in nonpregnant females. Cetirizine may be used when a second-generation antihistamine is needed. The lowest effective dose should be used.
Lactation	• Cetirizine is present in breast milk. • Drowsiness and irritability have been reported in breastfed infants exposed to antihistamines. In general, second-generation antihistamines (e.g., cetirizine) are less sedating as compared to their first-generation counterparts. If a breastfed infant is exposed to a second-generation antihistamine via breast milk, they should be monitored for irritability, jitteriness, or drowsiness. • When treatment with an antihistamine is needed in breastfeeding women for the treatment of rhinitis or urticaria, a second-generation antihistamine, such as cetirizine, is preferred. The

	lowest effective dose should be used. • Antihistamines may decrease maternal serum prolactin concentrations when administered prior to the establishment of breastfeeding.
Contraindications	• Hypersensitivity to cetirizine, hydroxyzine, levocetirizine, or any component of the formulation. • Canadian labeling: Additional contraindications: Hypersensitivity to piperazine derivatives; severe renal impairment (CrCl <10 mL/minute).
Monitoring Requirements	Relief of symptoms, sedation, mental alertness, and anticholinergic effects.
Precautions	**Concerns related to adverse effects**: -Pruritus: Rebound pruritus has been reported within several days after stopping cetirizine, usually after long-term (eg, months to years) use. **Disease-related concerns**: -Hepatic impairment: Use with caution; consider dosage adjustment. -Renal impairment: Use with caution; consider dosage adjustment. **Concurrent drug therapy issues:** -Sedatives: Effects may be potentiated when used with other sedative drugs or ethanol.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of urticaria treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health

Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for cetirizine.**

Table 10. Cetirizine HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Cetirizine	NICE[23]	July 8, 2014 – The NICE clinical knowledge summary on urticaria advises that the underlying cause of urticaria should be identified and managed, if possible. People with urticaria who need treatment should be offered a non-sedating antihistamine (for example, cetirizine, fexofenadine or loratadine) at the standard licensed dose, either as required until symptoms settle or regularly for up to 6 weeks. People with severe urticaria may also be given a short course of oral corticosteroids. If response to treatment is inadequate, the following options may be considered: -In adults, if there are no contraindications, the standard licensed dose of the first-choice antihistamine should be doubled (off-label use). -An alternative non-sedating antihistamine should be tried. -An additional sedative antihistamine (such as chlorphenamine) should be taken at night. -A topical antipruritic agent (such as calamine lotion) should be used to relieve itch. Referral to a dermatologist or immunologist is advised if symptoms are not well controlled on treatment or antihistamines are needed continuously for more than 6 weeks to control symptoms.
	CADTH	N/A
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – Cetirizine

Cetirizine is recommended as a first-line treatment of urticaria. It is given as 10 mg once daily for adults and can be increased to 10mg twice daily. It can be given for infants > 6 months. Its use is backed up by several HTA bodies namely NICE.

2.1.5 Levocetirizine

Information on levocetirizine is detailed in the table below:[24]

Table 11. Levocetirizine Drug Information

SCIENTIFIC NAME LEVOCETIRIZINE	
SFDA Classification	OTC
Trade Name(s) on Saudi Market	ALLERCET, LEVOZIN, ZOLIX, L-CET, XYZAL, LEVOZAL, LAYAL
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L50
Drug Class	ANTIHISTAMINES
Drug Sub-class	SECOND-GENERATION H1 RECEPTOR ANTAGONIST, PIPERIDINE DERIVATIVE
ATC Code	R06AE09
Pharmacological Class (ASHP)	ANTIHISTAMINES, 2ND GENERATION
DRUG INFORMATION	
Dosage Form	Syrup Oral solution Film-coated Tablet
Route of Administration	Oral Use
Dose (Adult) [DDD]*	**Urticaria, new onset (off-label use) and chronic spontaneous (labeled use):** New onset: Initial: 5 mg once daily. If symptom control is inadequate, may immediately increase to 5 mg twice daily.

	Chronic spontaneous: Initial: 5 mg once daily. If symptom control is inadequate, may increase in 5 mg/day increments every 1 to 4 weeks up to 10 mg twice daily; periodically reevaluate necessity for continued treatment.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	-Infants ≥6 months and Children ≤5 years: 1.25 mg once daily (in the evening); maximum daily dose: 1.25 mg/day -Children 6 to 11 years: 2.5 mg once daily (in the evening); maximum daily dose: 2.5 mg/day -Children ≥12 years and Adolescents: 5 mg once daily (in the evening); some patients may experience relief of symptoms with 2.5 mg once daily.
Maximum Daily Dose Pediatrics*	-Infants ≥6 months and Children ≤5 years: maximum daily dose: 1.25 mg/day. -Children 6 to 11 years: maximum daily dose: 2.5 mg/day.
Adjustment	**Altered Kidney Function:** - CrCl >80 mL/minute: No dosage adjustment necessary. - CrCl 50 to 80 mL/minute: 2.5 mg once daily. - CrCl 30 to 50 mL/minute: 2.5 mg once every other day. - CrCl 10 to 30 mL/minute: 2.5 mg twice weekly (every 3 or 4 days). - CrCl <10 mL/minute: Use is contraindicated. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	AGE

AGE (Age Edit)	For use in infants 6 months of age and above
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	N/A
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** diarrhea. **Most serious**: palpitation, tachycardia, syncope, epistaxis, pharyngitis.
Drug Interactions*	**Category X:** Aclidinium, Azelastine, Bromperidol, Cimetropium, Eluxadoline, Flunarizine, Glycopyrrolate, Glycopyrronium, Ipratropium, Kratom, Levosulpiride, Olopatadine, Orphenadrine, Oxatomide, Oxomemazine, Paraldehyde, Pitolisant, Potassium Chloride, Potassium Citrate, Pramlintide, Revefenacin, Thalidomide, Tiotropium, Umeclidinium.
Special Population	Older adult: Use with caution in the elderly.
Pregnancy	Levocetirizine is the active enantiomer of cetirizine. Guidelines for the use of antihistamines in the treatment of allergic rhinitis or urticaria in pregnancy are generally the same as in nonpregnant females. Second generation antihistamines may be used for the treatment of allergic rhinitis and urticaria during pregnancy; however, information related to the use of levocetirizine in

	pregnancy is limited and other medications may be preferred.
Lactation	Levocetirizine is the active enantiomer of cetirizine. It is not known if levocetirizine is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. When treatment of rhinitis and urticaria in breastfeeding women is needed, other agents are preferred.
Contraindications	-Known hypersensitivity to levocetirizine, cetirizine, or any component of the formulation. -End-stage renal disease (CrCl <10 mL/minute). -Hemodialysis -Infants and children 6 months to 11 years of age with renal impairment.
Monitoring Requirements	Creatinine clearance (prior to treatment for dosing adjustment).
Precautions	**Concerns related to adverse effects:** -CNS depression: May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). -Pruritus: Rebound pruritus has been reported within several days after stopping cetirizine, usually after long-term (eg, months to years) use; therefore, this may also occur with levocetirizine since it is the active enantiomer of cetirizine. **Disease-related concerns:**

	-Renal impairment: Levocetirizine is excreted primarily by the kidneys; use with caution in adults with mild to severe renal impairment; dosage adjustments may be needed. Use is contraindicated in end-stage renal disease (CrCl <10 mL/minute), patients undergoing hemodialysis, and in infants and children 6 months to 11 years of age with renal impairment. -Urinary retention: Urinary retention may occur; use with caution in patients with increased risk of urinary retention (including spinal cord lesions or prostatic hyperplasia); discontinue if urinary retention occurs.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

HTA reviews and recommendations of urticaria treatment options are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

CONCLUSION STATEMENT – Levocetirizine

Levocetirizine is recommended as a first-line treatment of urticaria. It is given as 5 mg once daily for adults and can be increased to 5 mg twice daily. It can be given for infants ≥ 6 months.

2.2 H2 Receptor Antagonists

2.2.1 Famotidine

Information on famotidine is detailed in the table below:[25,26]

Table 12. Famotidine Drug Information

SCIENTIFIC NAME FAMOTIDINE	
SFDA Classification	Prescription
Trade Name(s) on Saudi Market	FAMODAR
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L50
Drug Class	ANTIHISTAMINES
Drug Sub-class	HISTAMINE-2 (H2) RECEPTOR ANTAGONISTS
ATC Code	A02BB03
Pharmacological Class (ASHP)	HISTAMINE-2 (H2) RECEPTOR ANTAGONISTS
DRUG INFORMATION	
Dosage Form	Film-coated tablet
Route of Administration	Oral Use
Dose (Adult) [DDD]*	Use as additional therapy if insufficient response to full-dose H1 antihistamine. Oral: 20 mg twice daily given in combination with H1 antihistamine; a trial of 2 to 4 weeks is suggested to assess response.
Maximum Daily Dose Adults*	40mg/day
Dose (pediatrics)	N/A for this indication
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** IV:

	- CrCl ≥50 mL/minute: No dosage adjustment necessary. - CrCl <50 mL/minute: Administer 50% of usual dose or continue usual dose but increase the dosing interval to every 36 to 48 hours. Oral: refer to figure 5. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	AGE, CU, ST
AGE (Age Edit)	Not indicated for children < 12years.
CU (Concurrent Use Edit)	If symptoms are not sufficiently controlled with second-generation H1 antihistamines, H2 antihistamines may be added
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Second-line treatment after second-generation antihistamines
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** agitation, headache, diarrhea. **Most serious**: palpitation, nausea, thrombocytopenia, hallucination.
Drug Interactions*	**Category X:** Cefditoren, Cefuroxime, Dasatinib, Delavirdine, Dichlorphenamide, Levoketoconazole, Pazopanib, Risedronate, Sotorasib.
Special Population	-Older adults: Use with caution. -Pediatric: Use of gastric acid inhibitors, including proton pump inhibitors and H_2 blockers, has been associated with an

	increased risk for development of acute gastroenteritis and community-acquired pneumonia in pediatric patients.
Pregnancy	Famotidine crosses the placenta. Due to pregnancy-induced physiologic changes, renal clearance of famotidine may be increased.
Lactation	Famotidine is present in breast milk. The relative infant dose (RID) of famotidine is 2.2% when calculated using the highest breast milk concentration located and compared to an infant therapeutic dose of 0.5 mg/kg/day. In general, breastfeeding is considered acceptable when the RID of a medication is <10%. The RID of famotidine was calculated using a milk concentration of 0.072 mcg/mL, providing an estimated daily infant dose via breast milk of 0.011 mg/kg/day. This milk concentration was obtained following maternal administration of a single dose of famotidine 40 mg orally. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. When treatment with a histamine H_2 antagonist is needed, famotidine is one of the preferred agents due to its lower concentrations in breast milk.
Contraindications	-Serious hypersensitivity (e.g., anaphylaxis) to famotidine, other H2 antagonists, or any component of the formulation

	-When used for self-medication (OTC), do not use if trouble or pain when swallowing food, vomiting with blood, or bloody or black stools; allergic to other acid reducers; kidney impairment; coadministration with other acid reducers.
Monitoring Requirements	CBC, gastric pH, occult blood with GI bleeding.
Precautions	**Concerns related to adverse effects:** -Vitamin B_{12} deficiency: Famotidine and other H2RAs can reduce absorption of vitamin B_{12} and thus decrease serum concentrations. It is unclear of its role in causing function or clinical deficiencies. **Disease-related concerns:** -Gastric malignancy: Relief of symptoms does not preclude the presence of a gastric malignancy. -Kidney impairment: Use with caution; increased risk of QT prolongation; dosage adjustment may be required ***Dosage form specific issues:*** -Benzyl alcohol and derivatives: Some dosage forms may contain benzyl alcohol and/or sodium benzoate/benzoic acid; benzoic acid (benzoate) is a metabolite of benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; the "gasping syndrome" consists of metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction (including convulsions, intracranial hemorrhage), hypotension, and cardiovascular collapse; some data suggests that benzoate displaces bilirubin from protein binding sites; avoid or use dosage forms containing benzyl alcohol

	and/or benzyl alcohol derivative with caution in neonates.. OTC labeling: When used for self-medication (OTC), notify health care provider before use if any of the following are present: Frequent chest pain; frequent wheezing particularly with heartburn; nausea/vomiting; unexplained weight loss; stomach pain; heartburn >3 months; heartburn with light-headedness, sweating, or dizziness; chest pain or shoulder pain with shortness of breath; sweating; pain that spreads to arms, neck, or shoulders; light-headedness. Discontinue use and notify health care provider if heartburn continues or worsens, or if use is required >14 days.
Black Box Warning	N/A
REMS*	N/A

Table 13. Famotidine Oral Dosage Adjustments in Altered Kidney Function

CrCl (mL/min)	If usual dose is 10 mg twice daily	If usual dose is 20 mg once daily	If usual dose is 20 mg twice daily
CrCl ≥ 60	No dosage adjustment necessary		
CrCl 30 to < 60	10 mg once daily or 20 mg every other day	10 mg once daily or 20 mg every other day	20 mg once daily or 40 mg every other day
CrCl < 60	10 mg every other day	10 mg every other day	10 mg once daily or 20 mg every other day

HEALTH TECHNOLOGY ASSESSMENT (HTA)

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CONCLUSION STATEMENT – Famotidine

Famotidine is recommended as second-line treatment if symptoms of urticaria are not sufficiently controlled with second-generation H1 antihistamines. It is given as 20 mg twice daily for adults. It can be given for children > 12 years.

2.3 First-Generation H1 Receptor Antagonists

2.3.1 Hydroxyzine

Information on hydroxyzine is detailed in the table below:[27,28]

Table 14. Hydroxyzine Drug Information

SCIENTIFIC NAME HYDROXYZINE	
SFDA Classification	Prescription
Trade Name(s) on Saudi Market	ATARAX
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L50
Drug Class	ANTIHISTAMINES
Drug Sub-class	HISTAMINE H_1 ANTAGONIST, FIRST GENERATION, PIPERAZINE DERIVATIVE
ATC Code	N05BB01
Pharmacological Class (ASHP)	ANTIHISTAMINES, FIRST GENERATION
DRUG INFORMATION	
Dosage Form	Syrup Tablet
Route of Administration	Oral Use
Dose (Adult) [DDD]*	Initial: 10 to 25 mg at bedtime. May increase in 10 to 25 mg increments at weekly intervals if needed based on response and tolerability; daily dose may be administered at bedtime or in 3 to 4 divided doses.

	Some experts administer daily doses >100 mg in divided doses; do not exceed 200 mg/day
Maximum Daily Dose Adults*	200mg/day
Dose (pediatrics)	*__Age-directed dosing__: -Children <6 years: Oral: 12.5 mg 3 to 4 times daily. -Children ≥6 years and Adolescents: Oral: 12.5 to 25 mg 3 to 4 times daily. **Note:** Based on pharmacokinetic studies, dosing once daily (at bedtime) or twice daily may be adequate due to the long half-life. *__Weight-directed dosing:__ -Patient weight ≤40 kg: Oral: 2 mg/kg/day divided every 6 to 8 hours as needed; maximum dose: 25 mg/dose. **Note:** Based on pharmacokinetic studies, dosing once daily (at bedtime) or twice daily may be adequate due to the long half-life. -Patient weight >40 kg: Oral: 25 to 50 mg once daily at bedtime or twice daily.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** -CrCl ≥50 mL/minute: No dosage adjustment necessary (Ref). -CrCl 10 to <50 mL/minute: Administer ~50% of usual dose (Ref). -CrCl <10 mL/minute: Administer ~25% to 50% of usual dose. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling. In patients with primary biliary cirrhosis, change dosing interval to every 24 hours.
Prescribing edits*	CU, ST
AGE (Age Edit)	N/A

CU (Concurrent Use Edit)	If symptoms are not sufficiently controlled with H2 antihistamines, hydroxyzine may be added
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Third-line therapy
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** xerostomia. **Most serious**: drowsiness, respiratory depression, torsades de pointes.
Drug Interactions*	**Category X:** Aclidinium, Azelastine, Bromperidol, Cimetropium, Eluxadoline, Flunarizine, Glycopyrrolate, Glycopyrronium, Ipratropium, Kratom, Levosulpiride, Olopatadine, Orphenadrine, Oxatomide, Oxomemazine, Paraldehyde, Pitolisant, Potassium Chloride, Potassium Citrate, Pramlintide, Revefenacin, Thalidomide, Tiotropium, Umeclidinium.
Special Population	Older adult: May cause over sedation in older adults; avoid use.
Pregnancy	Hydroxyzine crosses the placenta. Possible withdrawal symptoms have been observed in neonates following chronic maternal use of hydroxyzine during pregnancy. Hydroxyzine is approved for pre- and postpartum adjunctive therapy to control emesis, reduce opioid dosage, and treat anxiety. Algorithms are available for the treatment of urticaria. First-generation oral antihistamines are generally not

	recommended for use in pregnant patients due to side effects.
Lactation	It is not known if hydroxyzine is present in breast milk. Drowsiness and irritability have been reported in breastfed infants exposed to antihistamines. Sedation has been reported in breastfed infants exposed to hydroxyzine. In general, if a breastfed infant is exposed to a first-generation antihistamine via breast milk, they should be monitored for irritability or drowsiness. Antihistamines may decrease maternal serum prolactin concentrations when administered prior to the establishment of lactation. Use of a second-generation antihistamine is preferred when an oral antihistamine is needed in lactating patients.
Contraindications	-Hypersensitivity to hydroxyzine or any component of the formulation. -Early pregnancy. -Prolonged QT interval. -History of torsade de pointes, including congenital long QT syndromes. -History of cardiac arrhythmias; significant electrolyte imbalance (eg, hypokalemia, hypomagnesemia). -Significant bradycardia. -Family history of sudden cardiac death.
Monitoring Requirements	Relief of symptoms, mental status and alertness, BP, rash (including worsening of pre-existing skin reactions), signs/symptoms of hypersensitivity reaction.
Precautions	**Concerns related to adverse effects:**

	-QT prolongation/torsades de pointes: Oral hydroxyzine is contraindicated in patients with a prolonged QT interval. **Disease-related concerns:** -Glaucoma: Use with caution in patients with narrow-angle glaucoma; condition may be exacerbated by cholinergic blockade. Screening is recommended. -Prostatic hyperplasia/urinary stricture: Use with caution in patients with prostatic hyperplasia and/or urinary stricture. -Respiratory disease: Use with caution in patients with asthma or chronic obstructive pulmonary disease (COPD).
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

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CONCLUSION STATEMENT – Hydroxyzine

Hydroxyzine is recommended as third-line treatment if symptoms of urticaria are not sufficiently controlled with H2 antagonists. It is given as 10 to 25 mg at bedtime. May increase in 10 to 25 mg increments at weekly intervals if needed based on response and tolerability. Note that the daily dose may be administered at bedtime or in 3 to 4 divided doses. Some experts administer daily doses >100 mg in divided doses; do not exceed 200 mg/day.

2.4 Corticosteroids

2.4.1 Prednisone

Information on prednisone is detailed in the table below:[29]

Table 15. Prednisone Drug Information

SCIENTIFIC NAME PREDNISONE	
SFDA Classification	Prescription
Trade Name(s) on Saudi Market	PREDONE
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L50
Drug Class	CORTICOSTEROID
Drug Sub-class	CORTICOSTEROID
ATC Code	H02AB07
Pharmacological Class (ASHP)	CORTICOSTEROID HORMONE RECEPTOR AGONIST
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral Use
Dose (Adult) [DDD]*	The optimal dosing strategy has not been defined; an example regimen is 20 to 60 mg daily initially, followed by a taper over 5 to 7 days. The total treatment duration should not exceed 10 days. Day 1: Administer 30 mg on day 1 as 10 mg at breakfast, 5 mg at lunch, 5 mg at dinner, and 10 mg at bedtime. Day 2: Administer 25 mg on day 2 as 5 mg at breakfast, 5 mg at lunch, 5 mg at dinner, and 10 mg at bedtime.

	Day 3: Administer 20 mg on day 3 as 5 mg at breakfast, 5 mg at lunch, 5 mg at dinner, and 5 mg at bedtime. Day 4: Administer 15 mg on day 4 as 5 mg at breakfast, 5 mg at lunch, and 5 mg at bedtime. Day 5: Administer 10 mg on day 5 as 5 mg at breakfast and 5 mg at bedtime. Day 6: Administer 5 mg on day 6 as 5 mg at breakfast.
Maximum Daily Dose Adults*	80 to 100 mg/day
Dose (pediatrics)	The specific dose is not available for urticaria in pediatrics. But the guidelines recommend individualizing dosing and using the lowest possible dose to control the condition. When dose reduction is possible, reduce dose gradually. Consider alternate day therapy for long-term therapy.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** The pharmacokinetics and pharmacodynamics of prednisone in kidney impairment are not well understood. Prednisolone (active metabolite) clearance is reduced ~40% in patients with uremia and is minimally dialyzable (≤17.5%); however, the clinical implications of these findings are unclear. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	CU, ST, PE
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	If symptoms are not sufficiently controlled with H2 antihistamines, prednisone may be added

G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Third line treatment
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	Day 1: Administer 30 mg on day 1 as 10 mg at breakfast, 5 mg at lunch, 5 mg at dinner, and 10 mg at bedtime. Day 2: Administer 25 mg on day 2 as 5 mg at breakfast, 5 mg at lunch, 5 mg at dinner, and 10 mg at bedtime. Day 3: Administer 20 mg on day 3 as 5 mg at breakfast, 5 mg at lunch, 5 mg at dinner, and 5 mg at bedtime. Day 4: Administer 15 mg on day 4 as 5 mg at breakfast, 5 mg at lunch, and 5 mg at bedtime. Day 5: Administer 10 mg on day 5 as 5 mg at breakfast and 5 mg at bedtime. Day 6: Administer 5 mg on day 6 as 5 mg at breakfast.
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** fluid retention, cardiac failure, atrial fibrillation, peptic ulcer. **Most serious**: cardiomegaly, osteonecrosis, osteoporosis, ulcerative esophagitis.
Drug Interactions*	**Category X:** Aldesleukin, BCG products, Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Desmopressin, Disulfiram, Macimorelin, Methotrimeprazine, Mifamurtide, Mifepristone, Mumps-Rubella- or Varicella-Containing Live Vaccines, Nadofaragene Firadenovec, Natalizumab, Ornidazole, Pimecrolimus, Poliovirus Vaccine (Live/Trivalent/Oral), Ritlecitinib, Ruxolitinib (Topical), Secnidazole, Tacrolimus (Topical),

	Talimogene Laherparepvec, Tertomotide, Typhoid Vaccine, Yellow Fever Vaccine.
Special Population	-Older adult: Use with caution in older adults with the smallest possible effective dose for the shortest duration. Pediatric: May affect growth velocity; growth and development should be routinely monitored in pediatric patients.
Pregnancy	Prednisone and its metabolite, prednisolone, cross the placenta. In the mother, prednisone is converted to the active metabolite prednisolone by the liver. Prior to reaching the fetus, prednisolone is converted by placental enzymes back to prednisone. As a result, the level of prednisone remaining in the maternal serum and reaching the fetus are similar; however, the amount of prednisolone reaching the fetus is ~8 to 10 times lower than the maternal serum concentration (healthy women at term). Hypoadrenalism may occur in newborns following maternal use of corticosteroids in pregnancy; monitor infants exposed to prolonged or high doses of prednisone in utero. Due to pregnancy-induced physiologic changes, clearance of prednisone may be increased (may be dose dependent) Prednisone is a preferred oral corticosteroid for the treatment of maternal conditions during pregnancy because placental enzymes limit passage to the embryo. **Prednisone ≤10 mg/day** is acceptable for use in pregnant patients with rheumatic and musculoskeletal diseases. Higher doses should be

	tapered to <20 mg/day with the addition of pregnancy compatible immunosuppressants. Stress dosing is not recommended during vaginal delivery. Corticosteroids may be used as needed for disease flares in pregnant patients with inflammatory bowel disease; however, maintenance therapy should be avoided. Uncontrolled asthma is associated with adverse events in pregnancy (increased risk of perinatal mortality, preeclampsia, preterm birth, low birth weight infants, cesarean delivery, and the development of gestational diabetes). Poorly controlled asthma or asthma exacerbations may have a greater fetal/maternal risk than what is associated with appropriately used asthma medications. Maternal treatment improves pregnancy outcomes by reducing the risk of some adverse events. Prednisone is recommended for use in fetal-neonatal alloimmune thrombocytopenia and pregnancy-associated immune thrombocytopenia.
Lactation	Prednisone and its metabolite, prednisolone, are present in breast milk. According to the manufacturer, prednisolone breast milk concentrations are 5% to 25% of the maternal serum levels, providing a total infant dose <1% of the maternal dose. Actual concentrations are dependent upon maternal dose. Peak concentrations of prednisone and prednisolone in breast milk occur ~2 to 3 hours after an oral maternal dose; the half-life in breast milk is 1.9 hours

	(prednisone) and 4.2 hours (prednisolone). The manufacturer notes that maternal use of high doses of systemic corticosteroids have the potential to cause adverse events in a breastfeeding infant (eg, growth suppression, interfere with endogenous corticosteroid production); therefore, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. The lowest effective dose should be used to minimize potential infant exposure via breast milk. Corticosteroids are generally considered acceptable in breastfeeding women when used in usual doses; however, monitoring of the breastfeeding infant is recommended. Prednisone is one of the oral corticosteroids preferred for use in breastfeeding women. If there is concern about exposure to the infant, some guidelines recommend waiting up to 4 hours after the maternal dose of an oral systemic corticosteroid before breastfeeding in order to decrease potential exposure to the breastfeeding infant.
Contraindications	-Hypersensitivity to prednisone or any component of the formulation; administration of live or live attenuated vaccines with immunosuppressive doses of prednisone; systemic fungal infections. -Significant drug interactions exist, requiring dose/frequency adjustment or avoidance.

	-Herpes simplex of the eye, measles, or chickenpox (except when being used for short-term or emergency therapy); peptic ulcer; nonspecific ulcerative colitis; diverticulitis; viral or bacterial infection not controlled by anti-infectives.
Monitoring Requirements	Blood pressure; weight; serum glucose; electrolytes; creatine kinase; growth in pediatric patients; presence of infection, bone mineral density; assess HPA axis suppression (eg, ACTH stimulation test, morning plasma cortisol test, urinary free cortisol test); Hgb, occult blood loss; chest x-ray (at regular intervals during prolonged therapy); IOP with therapy >6 weeks, eye examination (periodically during therapy.
Precautions	**Concerns related to adverse effects:** -Adrenal suppression: May cause hypercortisolism or suppression of hypothalamic-pituitary-adrenal (HPA) axis, particularly in younger children. **Disease-related concerns:** -Gastrointestinal disease: Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis [nonspecific]) due to perforation risk. -Head injury: Increased mortality was observed in patients receiving high-dose IV methylprednisolone; high-dose corticosteroids should not be used for the management of head injury. -Hepatic impairment: Use with caution in patients with hepatic impairment, including cirrhosis; effects may be enhanced. -Myasthenia gravis: Use may cause transient worsening of myasthenia

	gravis (MG) (eg, within first 2 weeks of treatment). -Ocular disease: Use with caution in patients with a history of ocular herpes simplex; corneal perforation has occurred; do not use in active ocular herpes simplex. -Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur. -Seizure disorders: Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. -Systemic sclerosis: Use with caution in patients with systemic sclerosis; an increase in scleroderma renal crisis incidence has been observed with corticosteroid use. Monitor BP and renal function in patients with systemic sclerosis treated with corticosteroids. -Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients. *Discontinuation of therapy: Withdraw therapy with gradual tapering of dose.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

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CONCLUSION STATEMENT – Prednisone

Prednisone is recommended as third-line treatment if symptoms of urticaria are not sufficiently controlled with H2 antagonists. The protocol edit is:

- Day 1: Administer 30 mg on day 1 as 10 mg at breakfast, 5 mg at lunch, 5 mg at dinner, and 10 mg at bedtime.
- Day 2: Administer 25 mg on day 2 as 5 mg at breakfast, 5 mg at lunch, 5 mg at dinner, and 10 mg at bedtime.
- Day 3: Administer 20 mg on day 3 as 5 mg at breakfast, 5 mg at lunch, 5 mg at dinner, and 5 mg at bedtime.
- Day 4: Administer 15 mg on day 4 as 5 mg at breakfast, 5 mg at lunch, and 5 mg at bedtime.
- Day 5: Administer 10 mg on day 5 as 5 mg at breakfast and 5 mg at bedtime.
- Day 6: Administer 5 mg on day 6 as 5 mg at breakfast

2.5 Leukotriene Receptor Antagonist

2.5.1 Montelukast

Information on montelukast is detailed in the table below:[30,31]

Table 16. Montelukast Drug Information

SCIENTIFIC NAME MONTELUKAST	
SFDA Classification	Prescription
Trade Name(s) on Saudi Market	MONTEL, LUKRA, MOTRINEX, MONTAS, MONCAS, SINGULAIR, EMCAST, YOCAIR.
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L50
Drug Class	LEUKOTRIENE RECEPTOR ANTAGONIST
Drug Sub-class	CYSTEINYL LEUKOTRIENE RECEPTOR ANTAGONISTS.
ATC Code	R03DC03

Pharmacological Class (ASHP)	CYSTEINYL LEUKOTRIENE RECEPTOR ANTAGONISTS.
DRUG INFORMATION	
Dosage Form	Film-coated tablet Chewable tablet Granules
Route of Administration	Oral Use
Dose (Adult) [DDD]*	10 mg once daily. Some experts suggest waiting ≥4 weeks before assessing efficacy.
Maximum Daily Dose Adults*	10mg/day
Dose (pediatrics)	Limited data available. Adolescents ≥15 years: Oral: 10 mg once daily.
Maximum Daily Dose Pediatrics*	10mg/day
Adjustment	**Altered Kidney Function:** No dosage adjustment necessary. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	AGE, CU, ST
AGE (Age Edit)	Adolescents ≥ 15 years
CU (Concurrent Use Edit)	If symptoms are not sufficiently controlled with second-generation H1 antihistamines, montelukast may be added
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	N/A
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Third 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:** headache. **Most serious**: conjunctivitis, otitis, acute bronchitis, epistaxis, trauma.
Drug Interactions*	**Category X:**

	Loxapine.
Special Population	N/A
Pregnancy	Based on available data, an increased risk of teratogenic effects has not been observed with montelukast use during pregnancy. Uncontrolled asthma is associated with adverse events on pregnancy (increased risk of perinatal mortality, preeclampsia, preterm birth, low-birth-weight infants, cesarean delivery, and the development of gestational diabetes). Maternal treatment improves pregnancy outcomes by reducing the risk of some adverse events (eg, preterm birth, gestational diabetes). Maternal asthma symptoms should be monitored monthly during pregnancy. Consider benefits and risks of treatment prior to use in pregnant patients
Lactation	Montelukast is present in breast milk. In general, breastfeeding is considered acceptable when the relative infant dose is <10%. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity to montelukast or any component of the formulation.
Monitoring Requirements	Neuropsychiatric events, including suicidal thinking/behavior.
Precautions	**Concerns related to adverse effects:** -Eosinophilia and vasculitis: In rare cases, patients may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with eosinophilic

	granulomatosis with polyangiitis (formerly known as Churg-Strauss); these clinical features may include eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy.
Black Box Warning (March 4, 2020)	• Serious neuropsychiatric events that may include suicidal thoughts or actions have been reported in patients taking montelukast. • Only use montelukast for allergic rhinitis in patients who have an inadequate response or intolerance to alternative therapies. • Consider risks and benefits when prescribing or continuing treatment. • Advise all patients of the risk of neuropsychiatric events when prescribing. • Discontinue and contact a health care professional immediately if changes in behavior or new neuropsychiatric symptoms, suicidal thoughts, or behavior occur. • Monitor for neuropsychiatric symptoms. • Events have occurred in patients with and without pre-existing psychiatric disease
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

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CONCLUSION STATEMENT – Montelukast

Montelukast is recommended as third-line treatment if symptoms of urticaria are not sufficiently controlled with H2 antagonists. It is given as 10 mg/day for adults and for adolescents 15 years of age and older.

2.6 Monoclonal Antibodies

2.6.1 Omalizumab

Information on omalizumab is detailed in the table below:[32,33]

Table 17. Omalizumab Drug Information

SCIENTIFIC NAME OMALIZUMAB	
SFDA Classification	Prescription
Trade Name(s) on Saudi Market	XOLAIR
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L50
Drug Class	Monoclonal Antibody
Drug Sub-class	Anti-IgE Monoclonal Antibody
ATC Code	R03DX05
Pharmacological Class (ASHP)	Anti-IgE Monoclonal Antibody
DRUG INFORMATION	
Dosage Form	Solution for injection in pre-filled syringe. Powder for solution for injection.
Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	-300 mg every 4 weeks; alternatively, may initiate at 150 mg every 4 weeks, although this dose has been associated with reduced efficacy. -If response is inadequate after 4 to 6 months, may consider dose escalation by increasing the dose and/or

	shortening the dosing interval to every 2 weeks (off-label) up to 600 mg every 2 to 4 weeks
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**Children ≥12 years and Adolescents**: SUBQ: 150 or 300 mg every 4 weeks. Dosing is not dependent on serum IgE (free or total) level or body weight.
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** There are no dosage adjustments provided in the manufacturer's labeling. **Hepatic Impairment:** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	AGE, MD, PA, ST
AGE (Age Edit)	Children ≥ 12 years and Adolescents.
CU (Concurrent Use Edit)	N/A
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Omalizumab can be prescribed by dermatologist or allergist
PA (Prior Authorization)	Omalizumab is an anti-IgE antibody indicated for the treatment of chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment.
QL (Quantity Limit)	N/A
ST (Step Therapy)	Fourth step
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** headache, erythema at injection site. **Most serious**: peripheral edema, urinary tract infection, fungal infection, anxiety, dermatitis.
Drug Interactions*	**Category X:**

	Loxapine.
Special Population	N/A
Pregnancy	Omalizumab crosses the placenta. Fetal exposure is dependent upon the maternal serum concentrations, placental integrity, newborn birth weight, and gestational age, generally increasing as pregnancy progresses. The lowest exposure would be expected during the period of organogenesis and the highest during the third trimester. In general, monoclonal antibodies should not be initiated during pregnancy. The option to continue treatment in patients who become pregnant during therapy should be considered as part of a shared decision-making process. Consider benefits and risks of treatment prior to use in pregnant patients.
Lactation	Omalizumab is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. Use of monoclonal antibodies for the treatment of asthma in lactating patients may be considered when conventional therapies are insufficient; omalizumab is considered possibly acceptable in for use in breastfeeding patients.
Contraindications	Severe hypersensitivity reaction to omalizumab or any component of the formulation.
Monitoring Requirements	Anaphylactic/hypersensitivity reactions (observe patients for 2 hours after the first 3 injections and 30 minutes after subsequent injections or in accordance

	with individual institution policies and procedures); baseline serum total IgE; FEV_1, peak flow, and/or other pulmonary function tests; monitor for signs of infection.
Precautions	**Concerns related to adverse effects:** -Cardiovascular effects: Cerebrovascular events, including transient ischemic attack and ischemic stroke, have been reported. -Eosinophilia and vasculitis: In rare cases, patients may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with eosinophilic granulomatosis with polyangiitis (formerly known as Churg-Strauss), a condition which is often treated with systemic corticosteroid therapy. Health care providers should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between omalizumab and these underlying conditions has not been established. -Fever/arthralgia/rash: Reports of a constellation of symptoms including fever, arthritis or arthralgia, rash, and lymphadenopathy have been reported with postmarketing use (symptoms resemble those seen in patients experiencing serum sickness, although circulating immune complexes or a skin biopsy consistent with a Type III hypersensitivity reaction were not seen with these cases). Onset of symptoms generally occurred 1 to 5 days following the first or subsequent doses. Discontinue therapy in any patient

	reporting this constellation of signs/symptoms. -Hypersensitivity/anaphylactoid reactions: Approximately 60% to 70% of cases reported occur within the first 3 doses; time to onset was within 2 hours for ~75% of cases; however, reactions have been reported with subsequent doses (after 39 doses) and with a time to onset of up to 4 days after administration. An epinephrine autoinjector should be prescribed for all patients receiving omalizumab. Discontinue therapy following any severe reaction. -Malignant neoplasms: Have been reported rarely with use in short-term studies; impact of long-term use is not known.
Black Box Warning	Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of omalizumab. Anaphylaxis has occurred as early as after the first dose of omalizumab but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, initiate omalizumab therapy in a health care setting and closely observe patients for an appropriate period of time after omalizumab administration. Health care providers administering omalizumab should be prepared to manage anaphylaxis, which can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care if symptoms occur.

	Selection of patients for self-administration of omalizumab should be based on criteria to mitigate risk from anaphylaxis.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of urticaria treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Omalizumab.**

Table 18. Omalizumab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Omalizumab	NICE[34]	June 8, 2015 – Omalizumab is **recommended** as an option as add-on therapy for treating severe chronic spontaneous urticaria in adults and young people aged 12 years and over only if: • The severity of the condition is assessed objectively, for example, using a weekly urticaria activity score of 28 or more. • The person's condition has not responded to standard treatment with H1-antihistamines and leukotriene receptor antagonists. • omalizumab is stopped at or before the fourth dose if the condition has not responded. • Omalizumab is stopped at the end of a course of treatment (6 doses) if the condition has responded, to establish whether the condition has gone into spontaneous remission, and is restarted only if the condition relapses. • Omalizumab is administered under the management of a secondary care specialist in dermatology, immunology, or allergy. • the company provides omalizumab with the discount agreed in the patient access scheme.

	CADTH[35]	May 7, 2015 – **Positive Recommendation**: The Canadian Drug Expert Committee (CDEC) recommends that omalizumab be listed for the treatment of adults and adolescents with chronic idiopathic urticaria (CIU) who remain symptomatic despite H1 antihistamine treatment, if the following clinical criterion and conditions are met: **Clinical criterion**: -Moderate to severe CIU who remain symptomatic (presence of hives and/or associated itching) despite optimum management with available oral therapies **Conditions**: -Substantial reduction in price -Six-month initial course of treatment
	HAS[36]	May 7, 2020 – **Positive Recommendation**: Favorable opinion on maintaining reimbursement as treatment of chronic spontaneous urticaria in the event of insufficient response to anti-H1 antihistamine treatments.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – Omalizumab

Omalizumab is recommended as a fourth-line treatment. It is an anti-IgE antibody indicated for the treatment of chronic idiopathic urticaria in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment. The initial dose is 150 mg every 4 weeks. If response is inadequate after 4 to 6 months, may consider dose escalation by increasing the dose and/or shortening the dosing interval to every 2 weeks (off-label) up to 600 mg every 2 to 4 weeks. Its use is backed up by several HTA bodies namely NICE, CADTH, HAS.

2.7 Immunosuppressants

2.7.1 Cyclosporine

Information on cyclosporine is detailed in the table below:[37,38]

Table 19. Cyclosporine Drug Information

SCIENTIFIC NAME CYCLOSPORIN	
SFDA Classification	Prescription
Trade Name(s) on Saudi Market	EFFYREN
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L50
Drug Class	IMMUNOSUPPRESSANTS
Drug Sub-class	CALCINEURIN INHIBITOR; IMMUNOSUPPRESSANT AGENT
ATC Code	L04AD01
Pharmacological Class (ASHP)	IMMUNOSUPPRESSANT AGENT
DRUG INFORMATION	
Dosage Form	Capsule, hard
Route of Administration	Oral Use
Dose (Adult) [DDD]*	Initial dose: 1 to 3 mg/kg/day in 2 divided doses. Titration: Increase by 0.5 mg/kg/day if insufficient response is seen after 4 weeks of treatment. Additional dosage increases may be made every 2 weeks if needed (maximum dose: 4 mg/kg/day). Discontinue if no benefit is seen by 6 weeks of therapy at the maximum dose. Once patients are adequately controlled, the dose should be decreased to the lowest effective dose.

	Treatment longer than 1 year is not recommended.
Maximum Daily Dose Adults*	4mg/Kg/day
Dose (pediatrics)	N/A for this indication
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** If serum creatinine increases 25% to 30% above baseline (measured on 2 separate occasions at least 2 weeks apart), or by ≥50% at any time during therapy, reduce dose by 25% to 50% and monitor serum creatinine every 2 weeks for 1 month. If serum creatinine does not decrease to within 25% to 30% of baseline, reduce dose further by 25% to 50% and monitor serum creatinine every 2 weeks for 1 month. If serum creatinine does not decrease to within 25% to 30% of baseline, discontinue cyclosporine. In patients receiving renal replacement therapies, consider temporary interruption of therapy or switching to an alternative agent to help promote renal recovery and preserve residual kidney function if other factors (eg, concurrent nephrotoxins, dehydration) contributing to decreased kidney function cannot be mitigated. Continued use should only be considered if the benefits outweigh risks of further kidney injury. **Hepatic Impairment:** metabolism is extensively hepatic (exposure is increased). Monitor blood concentrations; may require dose reduction.
Prescribing edits*	MD, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	N/A

G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Cyclosporin can be prescribed by dermatologist or allergist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Fourth step
EU (Emergency Use Only)	N/A
PE (Protocol Edit)	N/A
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most common:** headache, hypertension, tremor, nausea. **Most serious**: Urinary tract infection, pneumonia, sinusitis, confusion.
Drug Interactions*	Category X: Abrocitinib, Aliskiren, Asunaprevir, Atorvastatin, Baricitinib, BCG Products, Bilastine: P-glycoprotein / ABCB1 Inhibitors, Bosentan, Brivudine, Cladribine, Dengue Tetravalent Vaccine (Live), Deucravacitinib, Disulfiram, DOXOrubicin, Dronedarone, Elagolix, Erdafitinib, Fexinidazole, Foscarnet, Fusidic Acid, Grapefruit Juice, Lercanidipine, Lovastatin, Methotrimeprazine, Natalizumab, Ornidazole, Pimecrolimus, Simvastatin, Sirolimus, Tacrolimus.
Special Population	-Patients with systemic lupus erythematosus (SLE) undergoing hip or knee replacement surgery: Patients with ***severe*** SLE (referring to patients with severe organ manifestations such as nephritis) should not interrupt therapy when undergoing hip or knee replacement surgery. For patients with SLE ***without*** severe disease, hold cyclosporine for at least 1 week prior to surgery to reduce infection risk; therapy can be restarted once surgical wound shows evidence of healing (eg, no

	swelling, erythema, or drainage), sutures/staples are removed, and no ongoing nonsurgical site infections (typically ~14 days to reduce infection risk). -Transplant recipients: Make dose adjustments based on blood concentrations; dependent on organ transplanted, time after transplant, organ function, and CsA toxicity.
Pregnancy	Cyclosporine crosses the placenta. Cyclosporine is not associated with specific teratogenic effects, but maternal use may be associated with an increased risk of intrauterine growth restriction, small for gestational age babies, maternal hypertension, and preeclampsia. Premature births and low birth weight were consistently observed in pregnant transplant recipients (additional pregnancy complications also present). In utero exposure to cyclosporine has not been found to influence renal function or blood pressure in children followed up to 7 years of age.
Lactation	-Cyclosporine is present in breast milk. -Concentrations of cyclosporine in milk vary widely. -According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. Recommendations for breastfeeding in patients taking cyclosporine following a kidney transplant differ; generally breastfeeding may be considered with maternal use of maintenance doses

	Cyclosporine may be continued or initiated in patients with rheumatic and musculoskeletal diseases who are breastfeeding. Infants should be closely monitored. Infant drug levels should be measured if adverse events such as recurrent infections occur. Some formulations may contain alcohol which may be present in breast milk; the alcohol content should be taken into consideration prior to prescribing to a breastfeeding mother.
Contraindications	-Hypersensitivity to cyclosporine or any component of the formulation. -Rheumatoid arthritis and psoriasis patients with abnormal renal function, uncontrolled hypertension, or malignancies. Concomitant treatment with PUVA or UVB therapy, methotrexate, other immunosuppressive agents, coal tar, or radiation therapy are also contraindications for use in patients with psoriasis. Concurrent use with bosentan; rheumatoid arthritis and psoriasis patients with primary or secondary immunodeficiency excluding autoimmune disease, uncontrolled infection, or malignancy (excluding non-melanoma skin cancer).
Monitoring Requirements	-Monitor cyclosporine plasma concentrations, renal function (serum creatinine and BUN; especially with concomitant use of other nephrotoxic drugs), and BP periodically and following the addition, modification, or deletion of other medications. Monitor for hypersensitivity reactions (IV cyclosporine). Monitor for signs/symptoms of hepatotoxicity,

	secondary malignancy, diabetes mellitus, infection, progressive multifocal leukoencephalopathy (eg, hemiparesis, apathy, confusion, cognitive deficiencies, ataxia). Monitor for progressive cognitive or motor deficits; magnetic resonance imaging may be required for diagnosis of posterior reversible encephalopathy syndrome (PRES). -Baseline BP, serum creatinine (2 levels each), BUN, CBC, serum magnesium, potassium, uric acid, lipid profile. Every other week monitoring of BP, CBC, serum creatinine, and levels of BUN, uric acid, potassium, lipids, and magnesium during the first 3 months of treatment for psoriasis. Monthly monitoring is recommended after this initial period. Also evaluate any atypical skin lesions prior to therapy. Increase the frequency of BP monitoring after each alteration in dosage of cyclosporine. Consider test for tuberculosis (TB) infection (latent TB).
Precautions	**Disease-related concerns:** -Hepatic impairment: Cyclosporine has extensive hepatic metabolism and exposure is increased in patients with severe hepatic impairment. May require dose reduction. -Psoriasis: Appropriate use: If receiving other immunosuppressive agents, radiation or UV therapy, concurrent use of cyclosporine is not recommended.
Black Box Warning	-Should be prescribed only by physicians who have experience with immunosuppression in solid organ transplant recipients and can provide necessary follow-up and appropriate monitoring.

	-Coadministration with other immunosuppressants in kidney, liver, and heart transplant recipients, but risk of infection and neoplasia may be increased. -Increased risk for development of lymphomas and other malignancies, particularly those of the skin; avoid excess UV light exposure. -Increased risk appears related to the intensity and duration of immunosuppression rather than to the use of specific agents; oversuppression of the immune system may result in infection or malignancy; caution with regimens containing multiple immunosuppressants. -Sandimmune and Neoral are not bioequivalent and should not be interchanged without physician approval; Neoral (capsules and oral solution) has increased bioavailability compared with Sandimmune (capsules and oral solution). -For a given trough concentration, cyclosporine exposure will be greater with Neoral than with Sandimmune. -Sandimmune has decreased bioavailability compared with Neoral and erratic absorption; requires careful monitoring of blood levels and subsequent dosage adjustments. -Patients with psoriasis who have been treated with PUVA, methotrexate or immunosuppressants, UVB, coal tar, or radiation are at increased risk for skin malignancies, hypertension, and renal dysfunction.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

HTA reviews and recommendations of urticaria treatment options are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

CONCLUSION STATEMENT – Cyclosporin

Cyclosporin is recommended as fourth-line treatment of chronic idiopathic urticaria in adults who remain symptomatic despite H1 antihistamine. The initial dose is 1 to 3 mg/kg/day in 2 divided doses. This dose can be increased by 0.5 mg/kg/day if insufficient response is seen after 4 weeks of treatment. Additional dosage increases may be made every 2 weeks if needed (maximum dose: 4 mg/kg/day). Discontinue if no benefit is seen by 6 weeks of therapy at the maximum dose. Once patients are adequately controlled, the dose should be decreased to the lowest effective dose. Treatment longer.

2.8 Adrenergic Agonists

2.8.1 Epinephrine

Information on epinephrine is detailed in the table below [39]:

Table 20. Epinephrine Drug Information

SCIENTIFIC NAME EPINEPHRINE	
SFDA Classification	Prescription
Trade Name(s) on Saudi Market	SEPTANEST N, EPINOR, NOREPIRIN, NEVOLEEN, LEVOPHED
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	L50
Drug Class	ADRENERGIC AGONISTS
Drug Sub-class	ALPHA AND BETA-ADRENERGIC AGONISTS.
ATC Code	C01CA24

Pharmacological Class (ASHP)	ADRENERGIC AND DOPAMINERGIC AGENTS.
DRUG INFORMATION	
Dosage Form	Solution for injection Concentrate for solution for infusion Injection
Route of Administration	Intravenous Use
Dose (Adult) [DDD]*	Continuous infusion: IV: Initial: 0.1 to 0.2 mcg/kg/minute (or 8 to 16 mcg/minute for an 80 kg patient) administered with fluid resuscitation; starting dose is dependent on severity of anaphylaxis; titrate every 2 to 3 minutes by 0.05 mcg/kg/minute (or 4 mcg/minute) to response; usual dosing range: 0.01 to 0.2 mcg/kg/minute (or ~1 to 16 mcg/minute for an 80 kg patient). IM: 0.5 mg
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	-Infants <6 months: 0.01mg/kg IM -Infants ≥6 months and Children ≤6 years: 0.15mg IM -Children 6 to 12 years: 0.3 mg IM -Children ≥12 years and Adolescents: 0.5 mg IM. Repeat the intramuscular dose if there is no improvement in the patient's condition. Further doses can be given at 5 minutes intervals according to the patient's response
Maximum Daily Dose Pediatrics*	N/A
Adjustment	**Altered Kidney Function:** There are no dosage adjustments provided in the manufacturer's labeling.

	Hepatic Impairment: There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits*	MD, CU, ST
AGE (Age Edit)	N/A
CU (Concurrent Use Edit)	After H1 and H2 antihistamines and systemic steroids for severe angioedema.
G (Gender Edit)	N/A
MD (Physician Specialty Edit)	Epinephrine should be prescribed by allergist.
PA (Prior Authorization)	N/A
QL (Quantity Limit)	N/A
ST (Step Therapy)	Third 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:** anxiety, flushing, headache, nausea. **Most serious**: palpitation, tachycardia, tremor, respiratory difficulties.
Drug Interactions*	**Category X:** Blonanserin, Bromperidol, Ergot Derivatives, Isoproterenol, Kratom, Lisuride.
Special Population	-Older adults: Use with caution in older adults. -Pediatric: Lacerations, bent needles, and embedded needles have been reported in young children who are uncooperative during injection for hypersensitivity reaction. To minimize risk, hold the child's leg firmly in place and limit movement prior to and during injection. Although the manufacturers of auto-injectors recommend varying lengths of time for holding the device in the thigh (range: 2 to 10 seconds), longer times

	have occasionally resulted in injury. For all devices, the needle should remain in the thigh for the least amount of time as possible (~3 seconds).
Pregnancy	Epinephrine crosses the placenta. Epinephrine is recommended for the treatment of anaphylaxis in pregnant women. Specific dosing is not available; use with caution and monitor hemodynamic response. .
Lactation	It is not known if epinephrine is present in breast milk. Epinephrine is generally considered compatible in breastfeeding and is recommended for the treatment of anaphylaxis in breastfeeding women.
Contraindications	There are no contraindications listed in the manufacturer's labeling.
Monitoring Requirements	Heart rate, blood pressure (invasive blood pressure monitoring recommended while receiving continuous infusion); monitor site of infusion for blanching/extravasation; continuous cardiac monitoring required during continuous infusion. If using to treat hypotension, assess intravascular volume prior to and during therapy; support as needed; monitor for cardiac arrhythmias, hyperlactatemia, and hyperglycemia
Precautions	**Concerns related to adverse effects:** -Cardiac effects: May precipitate or aggravate angina pectoris or induce cardiac arrhythmias; use with caution especially in patients with cardiac disease or those receiving drugs that sensitize the myocardium. -Extravasation: IV administration: Vesicant; ensure proper needle or

	catheter placement prior to and during infusion. Avoid extravasation. -Pulmonary edema: Due to peripheral constriction and cardiac stimulation, pulmonary edema may occur. -Renal effects: Due to renal blood vessel constriction, decreased urine output may occur. **Disease-related concerns:** -Cardiovascular disease: Use with caution in patients with cardiovascular diseases (eg, arrhythmias, cerebrovascular disease, coronary artery disease, heart disease, hypertension). -Diabetes: Use with caution in patients with diabetes mellitus; may transiently increase blood glucose levels. -Hypovolemia: Correct blood volume depletion before administering any vasopressor. -Parkinson disease: Use with caution in patients with Parkinson disease; psychomotor agitation or temporary worsening of symptoms may occur. -Pheochromocytoma: Use with caution in patients with pheochromocytoma. -Thyroid disease: Use with caution in patients with thyroid disease..
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

HTA reviews and recommendations of urticaria treatment options are not available by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC).

CONCLUSION STATEMENT – Epinephrine

Epinephrin is recommended as third-line treatment after H1 and H2 antihistamines and systemic steroids for severe angioedema.

2.9 Other Drugs

2.9.1 Zafirlukast

Zafirlukast was approved by the FDA on September of 1996 and by the EMA. Zafirlukast is added if symptoms are not sufficiently controlled with second-generation H1 antihistamines especially in patients with NSAID intolerance or cold urticaria. Zafirlukast is to be given 20 mg twice daily.

2.9.2 Doxepin

Doxepin was approved by the FDA on March of 2010 and by the EMA in September 2006. Doxepin is added if symptomatic control is still not achieved with second-generation H1 antihistamines, H2 antihistamines, leukotriene receptor antagonist. Doxepin is to be given at the lowest dose, usually 10 mg to 25 mg.

Section 3.0 Key Recommendations Synthesis

- The management of new-onset urticaria depends upon severity and associated angioedema.
- The mainstay of treatment is avoidance of identified triggers. It is also recommended that patients avoid using aspirin, alcohol, and NSAIDs, as well as avoid wearing tight clothing, because these may worsen symptoms.
- If trigger avoidance is impossible, no trigger is identified, or symptom relief is needed despite trigger avoidance, nonsedating second-generation H1-antihistamines are first-line pharmacotherapy (Grade 2B). Second-generation H1 antihistamines such as loratadine, desloratadine, fexofenadine, cetirizine, and levocetirizine are relatively nonsedating at standard dosages and are dosed once per day.
- First-generation H1 antihistamines are faster acting and, in some cases, have parenteral forms. However, they require more frequent dosing and have more adverse effects, including sedation, confusion, dizziness, impaired concentration, and decreased psychomotor performance. Because of anticholinergic adverse effects, first-generation H1 antihistamines should be used with caution in older patients.
- There is no strong evidence that a particular antihistamine is superior.
- If symptoms are not sufficiently controlled with second-generation H1 antihistamines, the second step is implementation of one or more of the following additional strategies: the second-generation H1 antihistamine can be titrated up to two to four times the usual dose; a different second generation H1 antihistamine can be added; first-generation H1 antihistamines may be added at night-time; H2 antihistamines such famotidine may be added; and leukotriene receptor antagonists, such as montelukast and zafirlukast, can also be added, especially in patients with NSAID intolerance or cold urticaria.
- If symptomatic control is still not achieved, the third step is addition and titration of high-potency antihistamines as tolerated, such as hydroxyzine or the tricyclic antidepressant doxepin (possesses markedly more antihistaminic effect than diphenhydramine).
- The fourth step is referral to a subspecialist for use of immunomodulatory agents. There are a number of such agents, but the data on the effectiveness in urticaria for most are weak at best. The two agents with the most robust data are omalizumab and cyclosporine.

- In severe cases, corticosteroids such as prednisone (0.5 to 1 mg per kg per day) may be added for three to 10 days to control symptoms (Grade 2C).
- If systemic symptoms are suggested, especially when an identified trigger is associated with anaphylaxis (e.g., insect envenomation, certain foods), it may be prudent to prescribe epinephrine autoinjectors in sufficient numbers so that the patient will have one for home, one for work or school, and one for the car, as appropriate.
- Patients should follow up in two to six weeks to evaluate treatment success and tolerance.
- If an underlying cause of chronic urticaria is identified, the condition should be treated or the patient referred to an appropriate subspecialist.

Section 4.0 Conclusion

The recommendations provided in this report are intended to assist in the management of urticaria.

These recommendations should be used to support and not supplant decisions in individual patient management.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

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 period
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. Level of Evidence Description

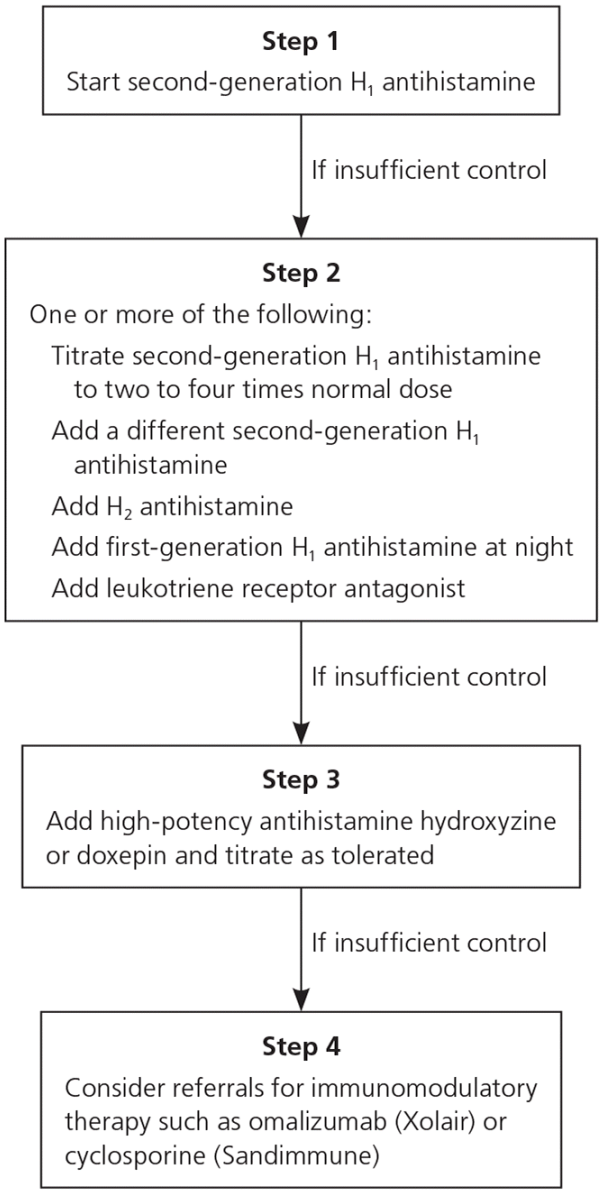
Grade of research	
A	Strongly recommend; good evidence
B	Recommend; at least fair evidence
C	No recommendation for or against; balance of benefits and harms too close to justify a recommendation
D	Recommend against; fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; evidence is lacking or of poor quality; benefits and harms cannot be determined
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies
Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search Methodology Terms

The following PubMed Search Methodology was opted:

Query	Filters	Search Details	Results
((Urticaria[MeSH Terms]) OR (Urticarias[Title/Abstract])) OR (Hives[Title/Abstract])	Meta-Analysis, Systematic Review, in the last 1 year	("urticaria"[MeSH Terms] OR "Urticarias"[Title/Abstract] OR "Hives"[Title/Abstract]) AND ((y_1[Filter]) AND (meta-analysis[Filter] OR systematicreview[Filter]))	22

Appendix D. Treatment Algorithm



NOTE: *If symptoms are severe, a short course (3 to 10 days) of systemic corticosteroids (e.g., oral prednisone, 0.5 to 1 mg per kg per day) may be added at steps 1, 2, or 3.*