# South East London

# Urticaria Treatment Pathway

**Guideline Summary**

This clinical guideline outlines the treatment pathway for adult patients with urticaria (with the exception for the use of Omalizumab in chronic spontaneous urticaria for 12 years and older)

## 1. Scope

This treatment pathway applies to adult patients with a diagnosis of urticaria (with the exception for the use of Omalizumab in chronic spontaneous urticaria for 12 years and older) and is primarily to set out the different treatment options available in secondary care

## 2. Rationale

This treatment pathway provides an evidence-based approach for the treatment of urticaria whilst maximising cost effectiveness and clinical outcome for use by all healthcare professionals involved in patient care.

## 3. Background

Chronic urticaria (CU) is a disease characterised by pruritic weals, angioedema or both occurring for at least 6 weeks. Around half of patients present with weals alone, 40% with weals and angio-oedema and 10% with angio-oedema only. It encompasses chronic spontaneous urticaria (CSU) and chronic inducible urticarias.

For information and guidance on management of urticaria in primary care please refer to the NICE Clinical Knowledge Summary (CKS) on urticaria.

Patients can have an inducible element to their urticaria which is triggered by heat, cold, pressure, vibration, water, ultraviolet light (UV), etc. These urticarias are induced reproducibly after a specific physical stimulus is applied, however there can be a certain degree of overlap between spontaneous and inducible urticarias.

**Unlicensed use of medicines: a number of medications recommended within the pathway are not licensed for use in urticaria and so are being used 'off-label'. These have been highlighted with an asterisk * throughout the document for information. Patients should be informed and consent to receive such treatments.**

**The use of Omalizumab within secondary care for the inducible urticarias listed in section 6 of the treatment pathway can be audited by the Dermatology, Allergy and Pharmacy departments as part of their annual clinical audit plan.**

See appendix 1 for prescribing responsibilities and RAG rating as per the South East London Joint Formulary.

## 4. Treatment Pathway For ALL types of urticaria

Primary care

**STEP 1: ALL PATIENTS**

- Non-sedating second-generation $H_1$ antihistamines at licensed dose e.g. cetirizine, loratadine (available over the counter), or fexofenadine 180mg OD (may be available as pharmacy only medicine)

If inadequate control: after 2-4 weeks, or earlier if symptoms are intolerable

**STEP 2: IF NON-RESPONDER [GP to prescribe]**

- Titrate dose of non-sedating H1 antihistamine up to four fold license* (cetirizine up to 20mg BD, loratadine 20mg BD or fexofenadine 360mg BD).
- Give lowest dose to control symptoms. Continuous dosing is more effective than on demand treatment.
- If the patient is getting little response, try a different antihistamine.
- Sedating antihistamines, although not routinely recommended, may be considered in some scenarios e.g. hydroxyzine 10-25mg at night can be added in patients who have symptoms interfering with sleep despite up dosing second generation antihistamine (for short term use only until better control can be achieved with 3rd line treatments).
- In patients who achieve complete symptom control for at least 3-6 months, you may consider attempting a stepwise reduction in dose and assessing response.

If inadequate control: after 2-4 weeks, or earlier if symptoms are intolerable

**STEP 3: IF NON-RESPONDER [GP to prescribe]**

- For CSU: Add montelukast* 10mg daily (as advised by NICE before consideration of omalizumab), if not contraindicated.
- Please note, montelukast can be *considered* in an inducible urticaria but is not essential prior to referral to secondary care

If inadequate control: after 4 weeks, or earlier if symptoms are intolerable move to step 4; or stop and refer

**STEP 4: IF NON-RESPONDER [GP to prescribe]**

- Consider adding H2 receptor antagonist e.g. famotidine up to 20mg BD or nizatidine up 150mg BD* (clinical preference; previously ranitidine up to 150mg BD/300mg daily, however currently unavailable).
- (Not essential for NICE criteria prior to omalizumab but useful to trial prior to referral to secondary care)
- Stop and refer if inadequate control after 2-4 weeks or earlier if symptoms are intolerable.

**IF SEVERE ANGIOEDEMA OR ACUTE-ON-CHRONIC FLARE**

- Consider pulsed prednisolone 0.5mg/kg for 3 days only
- Repeat up to 3-4 times/year if necessary
- Long term treatment with corticosteroids should never be used routinely

**IF NON-RESPONDER**

Refer via single point of referral ERS to community dermatology service

***Denotes off-label use of the medicine**

**Specialist Care**

**The decision on the choice of medication will be made by the specialist based on individual patient factors. The specialist will initiate these treatments.**

***Denotes off-label use of the medicine**

## 5. CHRONIC SPONTANEOUS URTICARIA (CSU)

**Chronic Spontaneous Urticaria**

**Trial of omalizumab if CSU severe despite optimal anti-mediator treatments in line with section 5.1**
See dosing schedule below

**ANGIOEDEMA WITHOUT WEALS**
Consider tranexamic acid* 500mg BD– 1.5gram TDS

**IF AUTOIMMUNE URTICARIA suspected (e.g. positive basophil histamine release assay)**
Consider ciclosporin* 4mg/kg/day starting dose reducing to 2mg/kg if possible (treatment duration generally up to 1 year).
If treatment failure/cautioned or contraindicated to omalizumab or ciclosporin, consider other immunosuppressive agents for CSU such as:

- Methotrexate* up to 25mg weekly (for 3/12 or longer)
- Mycophenolate mofetil* up to 1500mg BD or hydroxychloroquine* up to 200mg BD
- Azathioprine* 2mg/kg/day up to 2.5mg/kg/day in steroid dependent patients

Consider doxepin* 10-50mg at night in the appropriate context (CSU often coexists with anxiety and depression)

**If non-responder, reassess in a specialist urticaria clinic**

### 5.1 OMALIZUMAB IN CSU (12 years and older)

#### Eligibility and Dosing

See Figure A for full eligibility criteria and dosing recommendations for Omalizumab in CSU (non-angioedema predominant).

However, if the CSU is **angioedema predominant**, then follow usual eligibility criteria as per NICE TA339 (including angioedema activity score, AAS ≥ 28/week). Omalizumab should be given at 300mg every 4 weeks for a 6-month course and then stopped if the condition has responded in order to establish whether the condition has gone into spontaneous remission. It is restarted only if the condition relapses.

#### Administration

The first four doses of an initial course of omalizumab are administered as an outpatient in a specialist care setting in a dermatology, immunology or allergy clinic due to a very small risk of anaphylaxis. Following this, patients' may be suitable to self-administer treatment via a homecare delivery service.

**Patient reported outcomes (validated scoring tools):**

- **7-day Urticaria Activity Score (UAS7)** = In depth review of urticaria control on weekly basis.
- **7-day Angioedema Activity Score (AAS7)** = standard measure for assessing disease activity in patients with recurrent angioedema on weekly basis.
- **Urticaria Control Test (UCT)** = Overall control since last injection which can be a useful tool to use at the point of clinic consultation. *(NB. not a current requirement for eligibility to treatment but can be used at discretion of clinician*)
- **Dermatology Life Quality Index (DLQI)** = Alternative tool to assess disease impact on patient's life over the last one week. *(NB. primarily used for inducible urticaria, see section 6)*

## Figure A: OMALIZUMAB TREATMENT PATHWAY FOR CSU

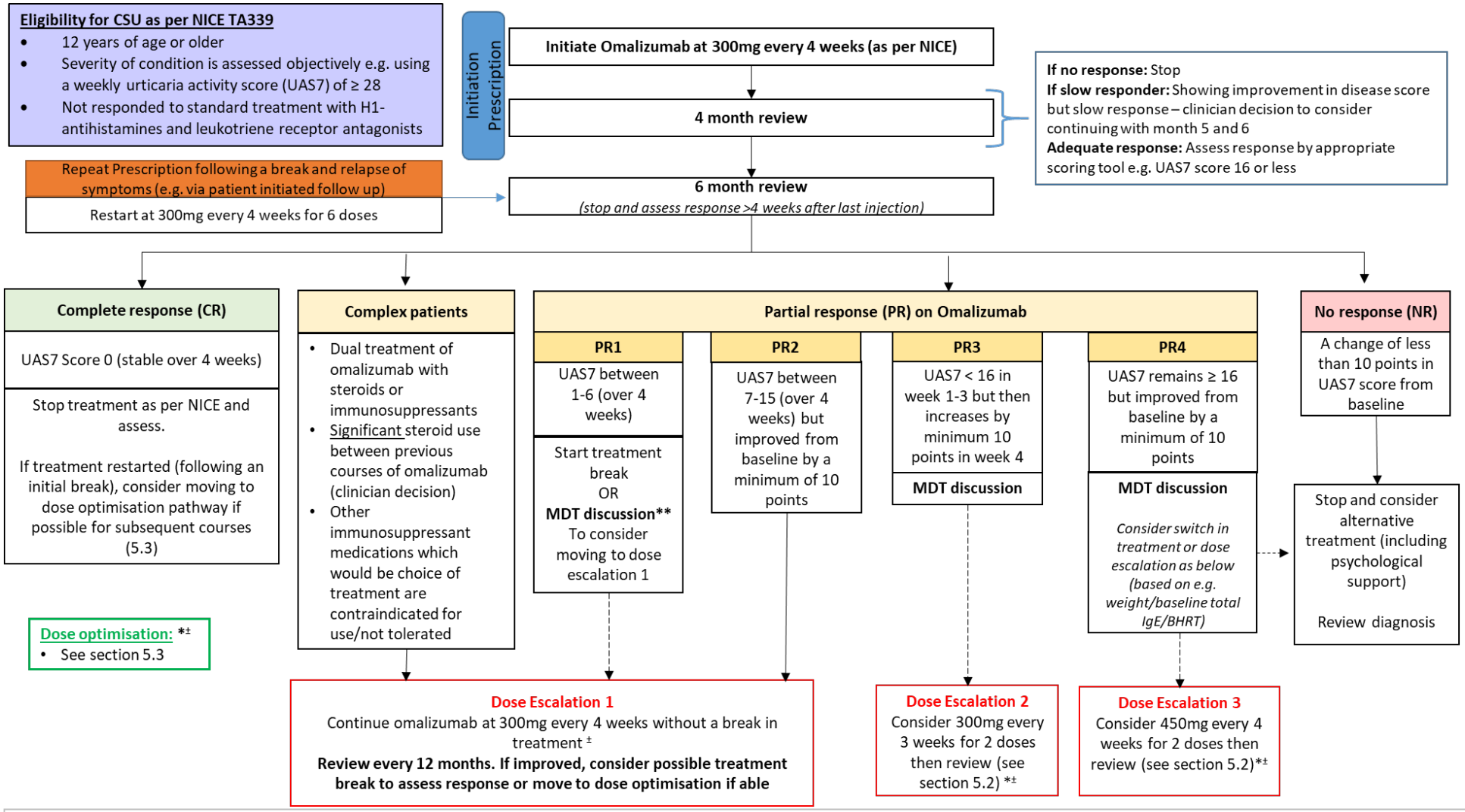


**Figure A Key:** * **Denotes off-label use of medicine; ± Denotes outside of NICE TA 339; > 'greater than'; ≥ 'greater than or equal to'; < 'less than'; ≤ 'less than or equal to'**

****UAS7 between 1-6 shows that the patient is well controlled but not completely controlled, therefore MDT decision to continue without break e.g. in patients showing gradual improvement in response where stopping would not be of benefit such as previous steroid dependence or immediate relapse to a more severe health state.**

*UAS7 score-based health states were defined as follows:* urticaria-free = 0; well-controlled urticaria = 1–6; mild =7–15; moderate =16–27; and severe urticaria=28–42.

## 5.2 DOSE ESCALATION

Dose escalation of omalizumab should be considered in patients with chronic spontaneous urticaria who are unable to achieve optimal primary response at the usual licensed dose and treatment duration. UAS7 scores should be monitored between doses and if an inadequate response is seen as specifically outlined in Figure A, then the patient will be discussed in an MDT and considered for the escalated dose recommended.
All patients that require an off-label dose for urticaria will be informed and will be counselled on any relevant risks and benefits; consent will be documented for those on this treatment pathway. However, it should be noted that omalizumab is licensed at higher doses for the treatment of allergic asthma (12 years and older) and has an overall good safety profile. Furthermore, due to the variable nature of chronic urticaria, patients throughout their management may at times become eligible for different pathways within Figure A.

| | **Dose** | **Recommended review** | **Licensed Dose** | **NICE approved** |
|---|---|---|---|---|
| **Dose Escalation 1** | Continue at 300mg every 4 weeks without a break in treatment | Review every 12 months to assess response. If responded, consider stopping to assess for possible remission or move to dose optimisation (if UAS7 scores are less than 7). | Yes * | No** |
| **Dose Escalation 2** | 300mg every 3 weeks | Give for 2 doses then review:<br>1. **No response** – review by specialist<br>2. **Stable UAS7 scores between doses -** continue 3 weekly dose with 6 monthly virtual review | No | No |
| **Dose Escalation 3** | 450mg every 4 weeks | Give for 2 doses then review:<br>**1. No response** – stop treatment and consider alternatives<br>**2. UAS7 less than 16**- continue 450mg dose with 6 monthly virtual review | No | No |

*licensing states *"Prescribers are advised to periodically reassess the need for continued therapy"*
**However, it should be acknowledged that NICE TA339 (Omalizumab for previously treated chronic spontaneous urticaria) does state: 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

## 5.3 DOSE OPTIMISATION

- To be done under the supervision and guidance of specialist team
- Extend dosing interval to 300mg every 5-6 weeks initially.
- If symptoms return before the end of the dosing interval, revert back to the last appropriate interval (i.e. to the point where symptoms returned)
- If asymptomatic, consider further extension in dosing interval (1-2 weekly increases at a time) as disease control allows. Review each dose change every 6 months and if asymptomatic, also consider a potential treatment break to assess if condition has gone into remission.

**Monitoring of patients on dose escalation (5.2) and dose optimisation (5.3) pathways will be as per the 'SEL Omalizumab for Chronic urticaria: Outcomes and Monitoring framework'.**

## 6. INDUCIBLE URTICARIA

***Denotes off-label use of the medicine**

**a) SYMPTOMATIC DERMOGRAPHISM**

1. Consider narrow band UVB phototherapy for at least 6 weeks
2. If DLQI ≥15 consider omalizumab* (150mg every 4 weeks increasing to 300mg every 4 weeks if necessary)

Omalizumab stopping criteria

Stop at or before the fourth dose if condition has not responded/DLQI does not reduce below 10 ₸

No increase in objective whealing threshold from 36g/mm$^2$ using a calibrated dermographometer

**b) CHOLINERGIC URTICARIA**

1. Consider danazol* 200-600mg daily (in divided doses) in men, propranolol* up to 40mg BD, or oxybutynin* 5mg 2-3 times a day increased to 5mg QDS if necessary. If failure of these consider propantheline* up to 30mg QDS or hyoscine butylbromide* 10mg TDS increased up to 20mg QDS. All of the above should be stopped if no response after 6 weeks at the maximum dose.
2. If DLQI ≥15 consider omalizumab* (150mg every 4 weeks increasing to 300mg every 4 weeks if necessary)

Omalizumab stopping criteria

Stop at or before the fourth dose if condition has not responded/DLQI does not reduce below 10 ₸

No subjective increase in exercise or heat tolerance

**c) DELAYED PRESSURE URTICARIA**

1. Consider dapsone* 50mg/day up to max. 150mg/day or sulfasalazine* 0.5-4g/day (if not aspirin sensitive). Stop after 6 weeks if no response at the maximum dose.
2. If DLQI ≥15 consider omalizumab* (150mg every 4 weeks increasing to 300mg every 4 weeks if necessary)

Omalizumab stopping criteria

Stop at or before the fourth dose if condition has not responded/DLQI does not reduce below 10 ₸

**d) COLD URTICARIA**

1. If DLQI ≥15 consider omalizumab* (150mg every 4 weeks increasing to 300mg every 4 weeks if necessary)
2. Consider ciclosporin* (4mg/kg for 4 weeks reducing by 1mg/kg every 6 weeks to zero for omalizumab non-responder. Longer treatment is an option)

Omalizumab stopping criteria

Stop at or before the fourth dose if condition has not responded/DLQI does not reduce below 10 ₸

No fall in temperature threshold using Temp Test

**e) SOLAR URTICARIA**

1. Consider ciclosporin* (4mg/kg for 4 weeks reducing by 1mg/kg every 6 weeks to zero. Longer treatment is an option)
2. If DLQI ≥15 consider omalizumab* (150mg every 4 weeks increasing to 300mg every 4 weeks if necessary)

Omalizumab stopping criteria

Stop at or before the fourth dose if condition has not responded/DLQI does not reduce below 10 ₸

No objective improvement in monochromator phototest thresholds

**Key:**

₸ In line with licensed use, omalizumab for an inducible urticaria should be stopped at 6 months if the condition has responded, and restarted only if the condition relapses

**≥** 'greater than or equal to'

## 7. OTHER URTICARIAS

***Denotes off-label use of the medicine**

a) IDIOPATHIC PRURITIS

- Consider amitriptyline* (up to 75mg ON), pregabalin* (up to 75mg BD), or gabapentin* (up to 600mg TDS) can be used for symptoms of dysesthesia/pruritus.
- Naltrexone* (initially 25mg daily increased to 50mg per day. Total weekly dose may be divided and given on 3 days of the week – max. 350mg per week) may rarely be used for idiopathic pruritus that has not responded to amitriptyline* (up to 75mg ON), pregabalin* (up to 75mg BD) or gabapentin* (up to 600mg TDS), reviewed every 3 months. Stop if no clinical response

b) URTICARIAL VASCULITIS OR AUTOINFLAMMATORY SYNDROMES

- Consider colchicine* 0.5mg BD up to 2.5mg daily (in divided doses)
- Hydroxychloroquine*, azathioprine*, methotrexate* or corticosteroids may also be considered

**Appendix 1**

**Traffic Light Status Information relevant for the indications included in this pathway:**

- **Red** – Specialist / hospital prescribing only.
- **Amber 1** – treatment can be initiated in primary care after a recommendation from an appropriate specialist
- **Amber 2** – Specialist initiation and supply followed by maintenance prescribing in primary care
- **Amber 3** – specialist initiation with ongoing monitoring required. Transfer of prescribing to the GP using either the approved SEL GP Information sheets where applicable or full shared care (drugs indicated with **).
- **Green** – specialist and non-specialist initiation

| Green | Amber 1 | Amber 2 | Amber 3 | Red |
|---|---|---|---|---|
| • Non-sedating second generation H1 antihistamines at licensed dose<br>• Non-sedating antihistamines up to four fold license<br>• Ranitidine<br>• Famotidine<br>• Nizatidine<br>• Montelukast<br>• Prednisolone | | • Tranexamic acid<br>• Colchicine<br>• Amitriptyline<br>• Oxybutynin<br>• Propantheline<br>• Hyoscine butylbromide<br>• Pregabalin<br>• Gabapentin<br>• Propranolol | GP Information sheets:<br>• Doxepin<br>• Danazol<br>• Naltrexone<br>Full shared care:<br>• Ciclosporin**<br>• Mycophenolate**<br>• Methotrexate **<br>• Hydroxychloroquine**<br>• Sulfasalazine**<br>Azathioprine** | Omalizumab<br>Dapsone |

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