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Unlicensed use of omalizumab for severe chronic inducible urticarias (solar urticaria, cold and heat urticaria, symptomatic dermographism, delayed pressure urticaria and cholinergic urticaria)

Recommendation	The CRG/GMMMG recommend restricted use of omalizumab in unlicensed indications of severe chronic inducible urticarias (solar urticaria, cold and heat urticaria, symptomatic dermographism, delayed pressure urticaria and cholinergic urticaria) in adults and young people aged 16-18 years who are transferred to adult services, as an option as add-on therapy only if: • the severity of the condition is assessed by objective scoring, for example, weekly urticaria activity score (UAS7) of 28 or more, Urticaria Control Test (UCT) below 12, Angioedema Control Test (AECT) below 10 and Dermatology Life Quality Index (DLQI) of more than 10; or objective severity testing methods and provocation threshold testing such as phototesting (solar urticaria), TempTest® (cold and heat urticaria), FricTest®/calibrated dermographometer (symptomatic dermographism), and pulse controlled ergometry (cholinergic urticaria) • the person's condition has not responded to standard treatment with H1-antihistamines (follow recommendations within the British Association of Dermatologists guidelines for management of people with chronic urticaria, 2021) • omalizumab is stopped at or before the 4th dose if the condition has not responded (DLQI does not reduce below 6, UAS7 does not reduce below 6, UCT does not improve to 12 or above, AECT does not improve above 10) • 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. In Greater Manchester this cohort of patients is under the specialist urticaria clinics provided by the dermatology services at the Northern Care Alliance NHS FT and the allergy service at the Manchester NHS FT, Wythenshawe Hospital.

Background	Omalizumab is a high cost drug which is commissioned by the Integrated Care System for this indication.[1] Omalizumab is a monoclonal antibody that targets IgE. It is licensed to treat autoimmune conditions including allergic asthma, chronic rhinosinusitis with nasal polyps and chronic spontaneous urticaria (CSU).[2] For the latter indication, NICE TA339 recommends omalizumab in adults and young people aged 12 and over as an add-on therapy for treating only severe forms of this disease not responding to standard treatment with H1-antihistamines and leukotriene receptor antagonists. The recommended dose for CSU is 300 mg by subcutaneous injection every four weeks[3]. Omalizumab is not licensed for use in chronic inducible urticaria (CIndU). CIndU is a subgroup of chronic urticaria (CU) characterized by the recurrence of itchy wheals and/or angioedema for longer than 6 weeks and is induced by specific physical or environmental stimuli (cold, heat, exercise, pressure, sunlight, vibration, water, etc.). According to the current international classification, it includes physical urticarias (symptomatic dermographism, delayed-pressure urticaria, exercise-induced urticaria, cold urticaria, heat urticaria, solar urticaria, and vibratory urticaria) and non-physical urticarias caused by exposure to specific stimuli (cholinergic urticaria, contact urticaria, and aquagenic urticaria). It is often difficult to define the exact type of CIndU. The diagnosis requires obtaining a detailed medical history of a patient with comprehensive information about predisposing factors, physical examination, and provocation testing (challenge tests).[4,5] The management of the condition starts with avoidance of identified triggers and use of 1st line pharmacological treatment with 2nd generation H1-antihistamines. The prevalence of CIndU is approximately 0.5% (15-25% of all cases of chronic urticaria).[6]
Efficacy and Safety	There is no NICE guideline for treatment of urticaria. British Association of Dermatologists (BAD) in their guideline for the management of people with chronic urticaria discuss treatment of the inducible form, although they note that evidence is based mainly on small case series and anecdotal evidence. BAD lists omalizumab as a 2nd line add-on treatment to 2nd generation H1-antihistamines, subject to licensing and funding. This is endorsed as a 'weak' recommendation meaning that risks and benefits of the intervention are finely balanced.[7] International guideline on definition, classification diagnosis and management of urticaria (including chronic spontaneous and inducible urticarias) states that omalizumab has been reported to be effective in CIndU and recommends its use in patients not responding to standard treatment with antihistamines.[8] There is limited amount of moderate and low strength evidence (low quality randomised controlled trials, retrospective analyses, observational case studies, case reports) available to support use of omalizumab in different types of CIndU. Common limitations include small sample size, limited follow up periods, lack of control group and retrospective approach. Maurer et al. (2018) conducted a systematic review of published evidence to determine the efficacy and safety of omalizumab in the treatment of CIndU. The evidence to support the use of omalizumab for the treatment of CIndU was strongest for symptomatic dermographism, cold contact urticaria, and solar urticaria, with little or no evidence for vibratory angioedema and aquagenic and contact urticaria. The authors stated that in general adverse events were at low level and rarely led to treatment discontinuation. Reported adverse events included suspected allergic reactions, gastrointestinal symptoms, injection site reactions, worsening urticaria, headache, dizziness, arthritis and fatigue.[9] Chicharro et al. (2017) conducted a retrospective review of case reports and case series describing the use of omalizumab to treat CIndU. The patients who benefited

	the most from treatment with omalizumab were those with symptomatic dermographism (n=8) where 7 patients (87.5%) had complete responses to omalizumab, 1 patient had a partial response, and there were no therapeutic failures and delayed pressure urticaria (n=17) where 13 patients (76%) achieved complete response, in 4 cases response was partial and there were no therapeutic failures. The least favourable outcomes were in patients with solar urticaria (n=16), where the complete response was achieved in 10 patients (62.5%). The authors reported absence of major adverse effects and a single case of fatigue and drowsiness.[10]
Cost Effectiveness/ Affordability	The proposed dose of omalizumab in CIndU is 300mg given subcutaneously every four weeks for up to six doses. The cost of a 150mg prefilled syringe is £256.15 and consequently £512.3 for a single 300mg dose (excluding VAT). The total cost for 24-week therapy (6 doses) equals £3,073.80 (excluding VAT).[11] It is estimated that up to 30 patients a year in GM might require this treatment, therefore maximum estimated cost for patients (if not requiring retreatment) per year is £92,214 (excluding VAT). It is unknown how many patients will require retreatment; however the condition usually lasts for a few years before it goes into complete remission. Omalizumab should be 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. Relapse is defined as UAS7 score of 16 or more, a DLQI score of 6 or more, a UCT score of 11 or less or an AECT score of 9 or less.
Monitoring	Clear record of patient figures, treatment outcomes, cases of retreatment and spend must be kept by the treatment provider and available on demand for purposes of audit or review of this commissioning statement.
Patient perspective	CIndU is a chronic condition which usually lasts several years, and often poses a great treatment challenge due to poor or no response to first-line therapy with 2nd generation of H1-antihistamines. CIndU can be debilitating and severely impacting patients' quality of life as avoidance of the offending trigger is often not feasible and requires major changes to everyday life. Therefore, there is high unmet need for an effective treatment. [9] Informed consent should be gained from the patient before treatment is started.

[1] NHS England, Specialised dermatology, Specialised dermatology services https://www.england.nhs.uk/wp-content/uploads/2013/06/a12-spec-dermatology.pdf

[2] SmPC for Xoalir 150mg solution for injection in pre-filled syringe, https://www.medicines.org.uk/emc/product/4725/smpc , accessed via eMC on 19/05/23

[3] NICE TA399, Omalizumab for previously treated chronic spontaneous urticaria, June 2015, https://www.nice.org.uk/guidance/ta339/chapter/1-Guidance

[4] Pozderac I. et al., Chronic inducible urticaria: classification and prominent features of physical and non-physical types, 2020, https://pubmed.ncbi.nlm.nih.gov/32975301/

[5] Magerl M et al. The definition, diagnostic testing, and management of chronic inducible urticarias–The EAACI/GA2LEN/EDF/UNEV consensus recommendations 2016 update and revision. Allergy 2016;71:780-802, https://pubmed.ncbi.nlm.nih.gov/26991006/

[6] DermNet, Chronic inducible urticaria, https://dermnetnz.org/topics/chronic-inducible-urticaria, accessed on 19/05/23

[7] British Association of Dermatologists, Guidelines for the management of people with chronic urticaria, 2021, https://academic.oup.com/bjd/article/186/3/398/6705777?login=false

[8] Zuberbier T et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy 2022;77:734-766, https://pubmed.ncbi.nlm.nih.gov/34536239/

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[10] Chicharro et al., Omalizumab in the treatment of chronic inducible urticaria, 2016, https://pubmed.ncbi.nlm.nih.gov/27717421/

[11] BNF online, https://bnf.nice.org.uk/drugs/omalizumab/medicinal-forms/ , accessed on 19/05/23