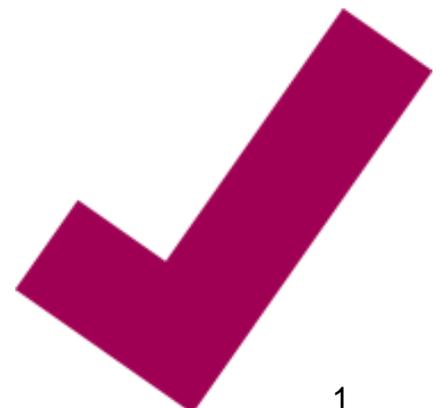


# **Interim Clinical Commissioning Policy Proposition: Adalimumab for Adults with Severe Refractory Uveitis**

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**Prepared by NHS England Specialised Services Clinical Reference Group for  
Specialised Ear and Ophthalmology CRG**

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# 1 Executive Summary

## Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

## Plain Language Summary

### About Uveitis

Uveitis is an uncommon group of conditions and describes inflammation of any structure within the eye. When very severe this may lead to vision loss. Uveitis accounts for around 10% of visual impairment registrations, which describe a spectrum of irreversible sight loss affecting both eyes to a level that precludes normal 'print' education or driving and includes total blindness.

Uveitis is commonly associated with a variety of inflammatory conditions affecting other organs. This policy is for the minority of cases with chronic sight threatening and visually disabling uveitis, refractory to conventional therapy.

### About current treatments

In severe cases treatment to try to prevent irreversible sight loss requires drugs that suppress immune cells (the white blood cell that protect us from infection and damage to our tissues) throughout the body. These are associated with significant short and long term side effects.

If conventional immunosuppressant treatments fail, the next step in treatment is the use of a group of drugs known as 'biologics'. These are very specialised and are designed to target specific molecules released during inflammation from cells and by doing so suppress inflammation.

### **About the new treatment**

Adalimumab is a humanised monoclonal antibody that binds to a biological mediator of inflammation called tumour necrosis factor alpha (TNF- $\alpha$ ).

### **What we have decided**

NHS England has carefully reviewed the evidence to treat uveitis with adalimumab. We have concluded that there is enough evidence to consider making the treatment available.

## 2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission Adalimumab for Adults with Severe Refractory Uveitis.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

NHS England proposes this interim policy whilst pending the publication of the NICE Multiple Technology Appraisal (MTA), expected in July 2017.

<https://www.nice.org.uk/guidance/indevelopment/gid-ta10007/documents>

## 3 Proposed Intervention and Clinical Indication

In severe cases of uveitis, treatment with immunosuppression is required to prevent sight-loss. First line therapy for such cases is with corticosteroids, usually in the form of prednisolone tablets. Corticosteroids have the important advantage of working quickly but have numerous side-effects especially at higher doses. For some patients, especially where only one eye is affected or where there is asymmetric bilateral disease, corticosteroids may instead be given as injections into or around the eye, an option potentially associated with complications such as cataract, glaucoma and infection.

Patients whose disease is not controlled on safe levels of prednisolone require second line therapy with immunosuppressant drugs, commonly an 'antiproliferative drug' such as mycophenolate mofetil and/or a 'calcineurin inhibitor' such as tacrolimus. These work in over 60% of patients. However, the remainder of patients are refractory to treatment or suffer serious treatment side effects.

This interim policy proposes that adalimumab be used in patients who are unable to

reduce their dose of prednisolone below 10mg per day having failed to respond (due to inefficacy or intolerance) to two 2nd line agents AND have evidence of worsening visual function (assessed by visual acuity and visual field).

## 4 Definitions

**Uveitis:** Uveitis is an uncommon group of conditions characterised by inflammation within the eye and describes inflammation of any structure within the eye that when very severe may cause visual loss.

**Biologic drug:** This term describes a range of medications which are derived from a variety of natural sources. They are not chemically synthesised and are typically manufactured using molecular biological techniques. A common example of a biologic drug is a monoclonal antibody.

**Steroid refractory:** Persistent inflammation despite treatment with  $\geq 10$ mg oral prednisolone daily for  $\geq 28$  days.

**Visual acuity:** The ability to discriminate between two adjacent objects. The smaller and closer the objects are that can be discriminated from each other, the better the visual acuity. This is quantified in clinical practice using a range of scoring systems which typically require the observer to read black letters of diminishing size projected against a white background.

**Visual field:** This is an assessment of peripheral vision. It quantifies the limits of peripheral visual perception when an eye is looking forward.

**Visual Function:** The quality of a person's vision. Central visual function is assessed by visual acuity and peripheral visual function is assessed by visual field.

## 5 Aims and Objectives

This policy proposition considered the interim commissioning position for the use of Adalimumab for severe refractory uveitis in adults, pending the publication of the NICE MTA appraisal currently in development (due for publication July 2017).

The objectives were to consider the evidence available and circumstances under which it would be considered appropriate and clinically effective for Adalimumab to be used in the treatment of potentially sight threatening severe refractory uveitis.

## 6 Epidemiology and Needs Assessment

It is estimated that in England, 220 adults per year would be eligible for treatment with adalimumab under this policy proposal. This is based on the following figures:

The prevalence of uveitis is approximately 115.3/100,000 and the incidence is approximately 52.4/100,000 (Gritz & Wong 2004).

Of all adult patients with uveitis in England we estimate 20% will have sight threatening disease requiring systemic therapy.

Of these, 60% will respond to standard immunosuppressant drugs including calcineurin inhibitors and anti-proliferative agents in combination with low-dose corticosteroids.

Of the 40% that do not respond to standard treatment, further escalation of treatment is available, prior to biologic use. This includes combining conventional 2nd line agents and using additional local therapies.

However, 10% remain unresponsive (estimated at around 220 new patients per annum in England) and will have ocular inflammation that will fulfil the eligibility criteria of this interim clinical commissioning policy for treatment with adalimumab.

## 7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

### **Summary of new evidence**

The efficacy and safety of adalimumab in the most sight-threatening forms of adult uveitis (specifically intermediate, posterior and panuveitis) has now been evaluated

in two randomised controlled trials, VISUAL I and VISUAL II. Both studies were double-blind, randomised, placebo-controlled phase 3 trials in the target population of the most sight-threatening forms of adult uveitis (described anatomically as intermediate, posterior, and panuveitic disease). VISUAL I investigated the use of adalimumab in patients with active uncontrolled uveitis, whereas VISUAL II investigated the use of adalimumab in patients with clinically 'quiescent' disease that was requiring high dose of maintenance corticosteroid therapy to maintain control. Both studies show significant evidence of benefit of adalimumab in terms of the primary endpoint (time to treatment failure) and that it is well tolerated with good safety profile in this population.

### **VISUAL I:**

#### ***Jaffe et al N Engl J Med 2016***

VISUAL I comprised 217 adult patients with active, non-infectious intermediate, posterior, or panuveitis despite >2 weeks of prednisolone (>10 mg/d to 60 mg/d). Active uveitis was defined as the presence of at least one of the following: active, inflammatory chorioretinal or retinal vascular lesion; anterior chamber cell grade >2+; or vitreous haze grade >2+. Patients were randomized 1:1 to adalimumab or placebo. The adalimumab group received an 80 mg baseline loading dose of adalimumab followed by 40 mg fortnightly for up to 80 weeks; all patients received prednisolone 60 mg/day that was tapered to 0 mg by week 15. The primary endpoint was time to treatment failure in at least one eye. Time to treatment failure was defined as at least one of the following: new, active, inflammatory vascular lesions; worsening of best-corrected visual acuity (BCVA) by >15 letters at or after week 6; inability to achieve >0.5+ anterior chamber (AC) cell grade or >0.5+ vitreous haze (VH) grade (at week 6); or 2-step increase in AC cell grade or VH grade (after week 6). Adverse events were monitored.

The median time to treatment failure was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Among the 217 patients in the intention-to-treat population, those receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% confidence interval, 0.36 to 0.70; P<0.001). Outcomes with regard to three secondary end points (change in

anterior chamber cell grade, change in vitreous haze grade, and change in best corrected visual acuity) were significantly better in the adalimumab group than in the placebo group ( $p=0.01$  for anterior chamber cell grade;  $p<0.001$  for vitreous haze grade;  $p=0.04$  for visual acuity). Although no new safety signals were detected, adverse events were reported more frequently in the adalimumab group compared with the placebo group (1052.4 vs. 971.7 adverse events per 100 person-years), with injection site reactions and allergic reactions being the most common. Only six events in the adalimumab group and three in the placebo group were directly attributed to trial intervention).

## **VISUAL II:**

### ***Nguyen et al Lancet 2016***

VISUAL II comprised 229 patients with inactive, non-infectious intermediate, posterior, or panuveitic uveitis controlled by 10-35 mg/day of prednisone. Patients were randomized to receive either subcutaneous adalimumab (loading dose 80 mg; biweekly dose 40 mg) or placebo, with a mandatory prednisone taper from week 2. The primary efficacy endpoint was time to treatment failure, a multicomponent endpoint encompassing new active inflammatory chorioretinal or inflammatory retinal vascular lesions, anterior chamber cell grade, vitreous haze grade, and visual acuity. Time to treatment failure was significantly longer in the adalimumab group compared with the placebo group (median not estimated [ $>18$  months] vs 8.3 months; hazard ratio 0.57, 95% CI 0.39-0.84;  $p=0.004$ ). The 40th percentile for time to treatment failure was 4.8 months in the placebo group and 10.2 months in the adalimumab group. The drug was well tolerated, with a similar rate of adverse events between groups and no new safety signals, showing that the drug was effective in enabling corticosteroid withdrawal in patients with inactive disease.

## **8 Proposed Criteria for Commissioning**

It is proposed that pending publication of the NICE MTA (expected July 2017) an interim policy is developed for adalimumab to be used in patients who have failed to taper to 10mg prednisolone daily despite failing (due to inefficacy or intolerance) two

2nd line agents AND evidence of worsening visual function (assessed by visual acuity and visual field).

Access to adalimumab would only be provided through existing specialised services commissioned for the provision of specialised ophthalmology.

### **Start Criteria**

Adults eligible for the use of adalimumab for the treatment of uveitis would meet the following criteria:

- Failure to achieve a daily oral prednisolone dose of <10mg daily despite prior treatment with two conventional second-line immunosuppressive agents for a minimum of 3 months (eg, mycophenolate mofetil, tacrolimus, methotrexate, cyclosporine A, azathioprine)
  
- Evidence of worsening visual function, defined as either:
  - A reduction in visual acuity by  $\geq 5$  logMAR letters (0.1 log units).  
[A logMAR (logarithm of the Minimal Angle of Resolution) chart comprises rows of letters and is used to estimate visual acuity. It is more accurate than the Snellen chart, which has traditionally been used by GPs and optometrists. It is the preferred assessment tool in research studies.]
  
- Severe immediately sight-threatening uveitis at risk of permanent loss of vision despite treatment with  $\geq 1.5$ g intravenous methyl prednisolone (in divided doses over 3 days) or 1mg/kg oral prednisolone for 1 week, defined as persistent:
  - Reduction of visual acuity by  $\geq 15$  logMAR letters (0.3 log units)
  - Vasculitis within the retinal vascular arcades
  - Standardization of Uveitis Nomenclature (SUN) vitreous haze score of  $\geq 2$
  - Central macular thickness  $>400\mu\text{m}$

Patients must be registered with NHS England's standard electronic contractual prior approval system confirming the start criteria are met.

## **In Treatment**

Response to therapy should be assessed after 3 months of therapy and re-assessed every 3 months whilst treatment continues. The following data points must be collected by for each patient every 3 months:

- Visual acuity measured in LogMAR
- Visual field scored as stable, worse or improved based on Humphrey, Goldmann or Octopus perimetry
- SUN anterior chamber activity and vitreous haze score
- Daily oral prednisolone dose
- Daily dose of conventional second-line immunosuppressive agents
- Frequency of topical steroid eye drops
- Intraocular pressure
- Frequency of topical antihypertensive drops
- Central macular thickness

Adults who respond to treatment with adalimumab will continue treatment for 18 months at which time a trial of treatment withdrawal will be undertaken. If relapse occurs, restarting adalimumab will be considered using the start criteria stated in this policy.

Response to treatment with adalimumab is defined as achieving one or more of the following criteria:

- Reduction in daily oral prednisolone dose by 5mg, or to  $\leq 10$ mg
- Reduction in conventional second-line immunosuppressive treatment
- For eyes with impaired visual acuity, an improvement in visual acuity by  $\geq 5$  LogMAR letters (0.1 log units)
- For eyes with reduced visual field, and improvement in visual field based on an assessment using Humphrey, Goldmann or Octopus perimetry
- For eyes with increased central macular thickness, a  $\geq 10\%$  reduction in central macular thickness

Serious adverse events must be reported to the Medicines and Healthcare products Regulatory Agency (MHRA) using the “yellow card system” which is the official

system for reporting adverse responses to medicines.

### **Stop Criteria**

Adalimumab for the treatment of uveitis is stopped using following criteria:

1. Failure to achieve the response criteria defined above after 3 months of treatment
2. Adverse reaction to adalimumab

## **9 Proposed Patient Pathway**

All patients fulfilling the criteria for this policy will be managed in a specialist centre with tertiary care facilities for inflammatory ocular diseases.

## **10 Proposed Governance Arrangements**

Adalimumab for the treatment of adults with severe refractory uveitis should only be initiated in centres commissioned for the treatment of specialised ophthalmology conditions.

## **11 Proposed Mechanism for Funding**

All treatments for uveitis up to and including the use of immunosuppressant therapy are to remain funded by Clinical Commissioning Groups.

Adalimumab will be commissioned and funded by NHS England Specialised Commissioning under existing arrangements for the provision of specialised ophthalmology services.

## **12 Proposed Audit Requirements**

Appropriate data fields will be included to enable collection of data through the NHS England's standard electronic contractual prior approval system.

## 13 Documents That Have Informed This Policy Proposition

- 1: Jaffe GJ, Dick AD, Brézin AP, Nguyen QD, Thorne JE, Kestelyn P, Barisani-Asenbauer T, Franco P, Heiligenhaus A, Scales D, Chu DS, Comez A, Kwatra NV, Song AP, Kron M, Tari S, Suhler EB. Adalimumab in Patients with Active Noninfectious Uveitis. *N Engl J Med*. 2016 Sep 8;375(10):932-43. doi: 10.1056/NEJMoa1509852. PubMed PMID: 27602665.
  
- 2: Nguyen QD, Merrill PT, Jaffe GJ, Dick AD, Kurup SK, Sheppard J, Schlaen A, Pavesio C, Cimino L, Van Calster J, Comez AA, Kwatra NV, Song AP, Kron M, Tari S, Brézin AP. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet*. 2016 Sep 17;388(10050):1183-92. doi: 10.1016/S0140-6736(16)31339-3.
  
3. One Wales Interim Commissioning Decision. Adalimumab (Humira®) for the treatment of adult patients with severe refractory non-infectious uveitis  
Date of advice: October 2016  
<https://openrepository.awttc.org/app/serve/resource/gbmr3178>
  
4. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop *Am J Ophthalmol*. 2005 Sep;140(3):509-16.

## 14 Date of Review

This document will be reviewed upon publication of the NICE MTA (TA10007), expected in July 2017

## 15 References

1: Jaffe GJ, Dick AD, Brézín AP, Nguyen QD, Thorne JE, Kestelyn P, Barisani-Asenbauer T, Franco P, Heiligenhaus A, Scales D, Chu DS, Comez A, Kwatra NV, Song AP, Kron M, Tari S, Suhler EB. Adalimumab in Patients with Active Noninfectious Uveitis. *N Engl J Med*. 2016 Sep 8;375(10):932-43. doi: 10.1056/NEJMoa1509852. PubMed PMID: 27602665.

2: Nguyen QD, Merrill PT, Jaffe GJ, Dick AD, Kurup SK, Sheppard J, Schlaen A, Pavesio C, Cimino L, Van Calster J, Comez AA, Kwatra NV, Song AP, Kron M, Tari S, Brézín AP. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet*. 2016 Sep 17;388(10050):1183-92. doi: 10.1016/S0140-6736(16)31339-3.