



# **Clinical Commissioning Policy: Infliximab (Remicade) as Anti-TNF Alpha Treatment Option for Paediatric Patients with Severe Refractory Uveitis**

Reference: NHS England D12/P/b

# OFFICIAL

## NHS England INFORMATION READER BOX

### Directorate

Medical	<b>Commissioning Operations</b>	Patients and Information
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

### Publications Gateway Reference:

**04347**

<b>Document Purpose</b>	Policy
<b>Document Name</b>	Infliximab (Remicade) as Anti-TNF Alpha Treatment Option for Paediatric Patients with Severe Refractory Uveitis
<b>Author</b>	Specialised Commissioning Team, NHS England
<b>Publication Date</b>	10 November 2015
<b>Target Audience</b>	Local Team Assistant Directors of Specialised Commissioning; Regional Team IFR Leads; Finance Leads; Local Team Pharmacists; Chairs of Clinical Reference Groups; Members of Clinical Reference Groups and registered stakeholders; Acute Trust Chief Executives; Acute Trust Medical Directors; Acute Trust Chief Pharmacists
<b>Additional Circulation List</b>	Regional Medical Directors; Regional Directors of Specialised Commissioning; Regional Clinical Directors of Specialised Commissioning; Regional Directors of Nursing
<b>Description</b>	NHS England will not routinely commission this specialised treatment in accordance with the criteria described in this policy.
<b>Cross Reference</b>	
<b>Superseded Docs (if applicable)</b>	D12/P/b Infliximab (Remicade) and Adalimumab (Humira) Anti-TNF Treatment Options for Paediatric Patients with Severe Refractory Uveitis published in July 2015
<b>Action Required</b>	
<b>Timing / Deadlines (if applicable)</b>	
<b>Contact Details for further information</b>	jeremyglyde@nhs.net for policy issues

### Document Status

This is a controlled document. Whilst this document may be printed, the electronic version posted on the intranet is the controlled copy. Any printed copies of this document are not controlled. As a controlled document, this document should not be saved onto local or network drives but should always be accessed from the intranet. **NB:** The National Health Service Commissioning Board was established on 1 October 2012 as an executive non-departmental public body. Since 1 April 2013, the National Health Service Commissioning Board has used the name NHS England for operational purposes.

## Contents

1	Executive Summary .....	4
	Policy Statement .....	4
	Equality Statement .....	4
	Plain Language Summary .....	4
2	Introduction .....	5
3	Definitions .....	5
4	Aims and Objectives .....	5
5	Epidemiology and Needs Assessment .....	5
6	Evidence Base .....	7
7	Rationale behind the Policy Statement .....	7
8	Criteria for Commissioning .....	7
9	Patient Pathway .....	7
10	Governance Arrangements .....	7
11	Mechanism for Funding .....	8
12	Audit Requirements .....	8
13	Documents which have informed this Policy .....	8
14	Links to other Policies .....	8
15	Date of Review .....	8
	References .....	8
	Appendix A .....	10

## 1 Executive Summary

### Policy Statement

NHS England does not routinely commission Infliximab (Remicade) as an Anti-TNF Alpha Treatment Options for Paediatric Patients with Severe Refractory Uveitis.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

### Equality Statement

NHS England has a duty to have regard to the need to reduce health inequalities in access to health services and health outcomes achieved as enshrined in the Health and Social Care Act 2012. NHS England is committed to fulfilling this duty as to equality of access and to avoiding unlawful discrimination on the grounds of age, gender, disability (including learning disability), gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender or sexual orientation. In carrying out its functions, NHS England will have due regard to the different needs of protected equality groups, in line with the Equality Act 2010. This document is compliant with the NHS Constitution and the Human Rights Act 1998. This applies to all activities for which NHS England is responsible, including policy development, review and implementation.

### Plain Language Summary

Uveitis is the term used to describe inflammation of any structure within the eye that when very severe may cause visual loss. Uveitis accounts for around 10% of visual impairment registrations.

In children, uveitis is commonly associated with juvenile arthritis where the eyes are affected in a similar way to the joints. Uveitis may occur before the onset of joint inflammation, and some children develop identical eye disease without ever having inflammation of the joints.

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

A potential next step in treatment is the use of a group of drugs known as 'biologics'. These are very specialised and are designed to focus on specific molecules released during inflammation from cells and by doing so suppress inflammation.

## 2 Introduction

Uveitis, or inflammation of the uveal tract, is a term used to describe inflammation inside the eye. It can lead to blindness either through direct damage to the light-sensitive retina, or through secondary complications such as glaucoma and cataracts. The Standardization of Uveitis Nomenclature (SUN) Working Group reported consensus diagnostic terminology, inflammation grading schema and outcome measures for uveitis in 2005.

## 3 Definitions

**Uveitis:** Uveitis is the term used to describe inflammation of any structure within the eye. This policy is for the minority of cases with chronic sight threatening and visually disabling uveitis, refractory to topical and oral steroids and methotrexate.

**Infliximab:** Also known as Remicade is an anti-TNF alpha treatment licensed and NICE approved for the treatment of adults with inflammatory arthritis.

## 4 Aims and Objectives

This policy aims to set out the NHS England Commissioning position for the use of Infliximab (Remicade) as an Anti-TNF Alpha Treatment Options for Paediatric Patients with Severe Refractory Uveitis

## 5 Epidemiology and Needs Assessment

Children with Uveitis represent between 2% and 6% of the total uveitis population. The incidence of childhood uveitis in the general population of North America and Europe is estimated at 4.3-6/100,000, children, and the prevalence at 30/100,000; with the lowest incidence in the youngest children (Heiligenhaus et al 2013).

### **Association of Childhood Uveitis with Juvenile Idiopathic Arthritis**

Uveitis in childhood can develop in association with various inflammatory arthropathies and in particular Juvenile Idiopathic Arthritis (JIA). Before the advent of uveitis screening for patients with JIA, and modern forms of treatment, rates of blindness in childhood uveitis were up to 30%. Despite recent changes in management and widespread screening, the risk of irreparable visual impairment remains high for such children.

20-25% of all uveitis in children is associated with Juvenile Idiopathic Arthritis (JIA). 12-38% of patients with JIA will develop uveitis within 7 years following the onset of uveitis.

Asymptomatic chronic anterior uveitis (CAU) associated with JIA has long been recognised as an important cause of visual loss in childhood with high levels of complications compared to other forms of anterior uveitis. The incidence of bilateral disease is between 67-85%. 0.5% of childhood blindness in England and Wales is caused by uveitis (Rahi 2013) – approximately 100 new presentations per annum, with other children visually impaired from complications of uveitis such as cataract and glaucoma.

Uveitis may be presenting feature of JIA in 3-7% of patients (Dana MR 1997, Kanski JJ 1977), and in 50% develops simultaneously or within 6 months of the onset of arthritis (Heiligenhaus 2007).

### **Chronic Uveitis in Childhood not associated with JIA**

A group of children exists with ocular disease clinically indistinguishable from JIA-U, who may or may not later develop JIA. This group is less well described. In the general population there are equal numbers of patients with idiopathic uveitis as patients with JIA-uveitis

## **Effects of Visual Impairment on Childhood Development**

Visual impairment in childhood is a major disability, impacting on motor and cognitive development, education and emotional development and social relationships. There is a significantly increased prevalence of autism in visually impaired children. The effects are felt by the whole family and the child's life chances and opportunities are severely restricted.

## **6 Evidence Base**

NHS England considered the available clinical evidence as described by the Clinical Reference Group. NHS England concluded that there was not sufficient evidence to support the routine commissioning of this treatment for the indication. In the interests of transparency the clinical case that was put to NHS England by the CRG is set out in Appendix A.

## **7 Rationale behind the Policy Statement**

The use of Infliximab (Remicade) as an anti-TNF alpha treatment options for paediatric patients with severe refractory uveitis has been considered by NHS England who concluded that there was not sufficient evidence to support the routine commissioning of this treatment/procedure.

## **8 Criteria for Commissioning**

NHS England does not routinely commission Infliximab (Remicade) as an anti-TNF alpha treatment options for paediatric patients with severe refractory uveitis.

## **9 Patient Pathway**

Not applicable

## **10 Governance Arrangements**

Not applicable

## 11 Mechanism for Funding

NHS England will not routinely fund Infliximab (Remicade) as an anti-TNF alpha treatment options for paediatric patients with severe refractory uveitis.

## 12 Audit Requirements

Not applicable

## 13 Documents which have informed this Policy

See reference list below

## 14 Links to other Policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

## 15 Date of Review

This policy will be reviewed in April 2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

## References

1. Kotaniemi K, Säilä H, Kautiainen H. Long-term efficacy of adalimumab in the treatment of uveitis associated with juvenile idiopathic arthritis. *Clin Ophthalmol.* 2011;5:1425-9
2. Stanbury RM, Graham EM. Systemic corticosteroid therapy--side effects and their management. *Br J Ophthalmol.* 1998 Jun;82(6):704-8.
3. Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids *Curr Opin Ophthalmol.* 2000 Dec;11(6):478-83.
4. Thorne JE<sup>1</sup>, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with

- topical corticosteroids. *Ophthalmology*. 2010 Jul;117(7):1436-41. doi: 10.1016/j.ophtha.2009.12.003.
5. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert Panel Recommendations for the Use of Anti-Tumor Necrosis Factor Biologic Agents in Patients with Ocular Inflammatory Disorders. *Ophthalmology*. 2013 Dec 17. pii: S0161-6420(13)00893-2. doi: 10.1016/j.ophtha.2013.09.048. [Epub ahead of print]
  6. Cordero-Coma M, Yilmaz T, Onal S Systematic review of anti-tumor necrosis factor-alpha therapy for treatment of immune-mediated uveitis. *Ocul Immunol Inflamm*. 2013;21(1):19-27. doi: 10.3109/09273948.2012.723107
  7. Tugal-Tutkun I, Ayranci O, Kasapcopur O, Kir N. Retrospective analysis of children with uveitis treated with infliximab. *J AAPOS*. 2008 Dec;12(6):611-3
  8. Sukumaran S, Marzan K, Shaham B, Reiff A. High dose infliximab in the treatment of refractory uveitis: does dose matter? *ISRN Rheumatol*. 2012;2012:765380.
  9. Tynjälä P, Kotaniemi K, Lindahl P, Latva K, Aalto K, Honkanen V, Lahdenne P. Adalimumab in juvenile idiopathic arthritis-associated chronic anterior uveitis. *Rheumatology (Oxford)*. 2008 Mar;47(3):339-44.
  10. Simonini G, Taddio A, Cattalini M, Caputo R, de Libero C, Parentin F, Pagnini I, Lepore L, Cimaz R. Superior efficacy of Adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug: Adalimumab as starting anti-TNF-alpha therapy in childhood chronic uveitis. *Pediatr Rheumatol Online J*. 2013 Apr 15;11(1):16.
  11. Magli A, Forte R, Navarro P, Russo G, Orlando F, Latanza L, Alessio M. Adalimumab for juvenile idiopathic arthritis-associated uveitis. *Graefes Arch Clin Exp Ophthalmol*. 2013 Jun;251(6):1601-6.
  12. Simonini G, Taddio A, Cattalini M, Caputo R, De Libero C, Naviglio S, Bresci C, Lorusso M, Lepore L, Cimaz R. Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. *Arthritis Care Res (Hoboken)*. 2011 Apr;63(4):612-8.
  13. Caspi RR Understanding autoimmune uveitis through animal models. The Friedenwald Lecture. *Invest Ophthalmol Vis Sci*. 2011 Mar 30;52(3):1872-9. doi: 10.1167/iovs.10-6909. Print 2011 Mar.

14. Dick AD, Forrester JV, Liversidge J, Cope AP. The role of tumour necrosis factor (TNF-alpha) in experimental autoimmune uveoretinitis (EAU). *Prog Retin Eye Res.* 2004 Nov;23(6):617-37.
15. Simonini G, Druce K, Cimaz R, Macfarlane GJ, Jones GT. Current evidence of anti-tumor necrosis factor  $\alpha$  treatment efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach of individual drugs. *Arthritis Care Res (Hoboken).* 2014a Jul;66(7):1073-84.
16. Simonini G, Katie D, Cimaz R, Macfarlane GJ, Jones GT. Does switching anti-TNF $\alpha$  biologic agents represent an effective option in childhood chronic uveitis: the evidence from a systematic review and meta-analysis approach. *Semin Arthritis Rheum.* 2014b Aug;44(1):39-46.

## Appendix A

NHS England considered the available clinical evidence as described by the Clinical Reference Group. NHS England concluded that there was not sufficient evidence to support the routine commissioning of this treatment for the indication. In the interests of transparency the clinical case that was put to NHS England by the CRG is set out below for information.

*“A type of biologic called anti-TNF (either Infliximab or Adalimumab) is now the standard of care for severe cases across the world. Anti TNF agents have superseded alternative drugs to steroids in the treatment of juvenile arthritis, as they have been shown to be more effective and to have fewer side effects. Anti-TNF agents have also been observed to be effective against uveitis when given for the treatment of arthritis.*

*A randomized controlled trial, the SYCAMORE study, which was specifically for children who have uveitis associated with juvenile arthritis, compared the efficacy of Adalimumab to placebo, has stopped recruitment to the trial on the grounds of efficacy.*

*The aim of treatment is to minimise chronic ocular inflammation and thereby reduce the risks of ocular complications leading to visual impairment.*

## OFFICIAL

*Induction of early remission of inflammation is felt to be important in preventing long term persistence of inflammation with associated complications. Initial treatment for children with mild disease is local (topical steroid eye drops, peri- and intra-ocular steroid injections), followed by systemic treatment and, if initial treatment fails to induce remission, with systemic steroids.*

*Children in whom disease remission is not induced by treatment with topical, peri-ocular or systemic steroid, or who require prolonged treatment with high dose steroid in order to maintain remission, then proceed to treatment with a second line agent.*

*Historically, the use of systemic corticosteroids in uveitis was often in high doses for long periods of time (Howe et al 1994). These are associated with severe side effects in children, including dermatological, haematological, endocrine, metabolic, musculoskeletal and gastrointestinal impact (Stanbury et al 1998). Furthermore, topical ophthalmic, oral, and intravenous corticosteroids have also been associated with ocular side effects such as increased intraocular pressure, development of cataract, glaucoma, and even retinal and choroidal emboli (Carnahan & Goldstein 2000, Thorne et al 2010). Therefore, the minimum dose necessary to control the disease should be given and prolonged use avoided.*

*The standard initial second line agent, for both JIA and uveitis, is immunosuppressants such as Methotrexate (MTX). There exists a significant group of children in whom uveitis cannot be controlled by tolerated levels of systemic steroid and conventional immunosuppressants methotrexate. The agents currently available for use in children whose disease is not controlled by tolerated doses of systemic steroid and methotrexate include Ciclosporin, Mycophenolate, Azathioprine, Tacrolimus and Cyclophosphamide, which are all themselves associated with severe side effects in children.*

### **Anti-TNF Agents**

## OFFICIAL

*These new agents are antibodies directed against Tumour Necrosis Factor  $\alpha$ , which is a cytokine which has been shown experimentally to be involved in the pathogenesis of uveitis. The currently available agents are Etanercept, Adalimumab, Infliximab, Golimumab and Certolizumab.*

*Of these treatments the following licensing and NICE approval exists:*

- Etanercept is licensed and approved by NICE for use in children with JIA;*
- Adalimumab is licensed for use in JIA but is not currently NICE-approved*
- Infliximab and Adalimumab are licensed and NICE-approved in adults with inflammatory arthritis*
- Certolizumab and Golimumab are licensed but not currently NICE-approved in Adults with inflammatory arthritis.*

*Trial data suggests that Etanercept has no impact on disease activity in JIA uveitis. The onset of uveitis in a child on Etanercept for the treatment of JIA can therefore be an indication to switch to an alternative agent. This agent is therefore not suitable as the first line anti-TNF for the treatment of JIA-Uveitis (JIA-U) and similar uveitis not associated with JIA.*

*Adalimumab and Infliximab have been shown in randomised controlled trials (RCTs) to be highly effective in the treatment of JIA, with relatively few reported side effects. They are usually given in conjunction with methotrexate to optimise their effect. In addition to their effect in JIA, Adalimumab and Infliximab are felt by the international ophthalmology community to be highly effective in the treatment of JIA-U, and clinically similar childhood uveitis not associated with JIA (see supporting correspondence) Their use is supported by expert opinion, many reviews (Levy-Clarke et al 2013, Cordero-Coma et al 2013) published data and the Scottish Uveitis Network.*

*The use of Adalimumab and Infliximab has already become the standard-of-care in specialised uveitis services across the world. The effect of Adalimumab and Infliximab on JIA-U has not been reported by the RCTs of their use in JIA,*

*as children with JIA-U were excluded from taking part in these studies. The Sycamore trial (see below) is was specifically addressing the use of adalimumab in JIA-U but excluded other forms of paediatric uveitis including those with uveitis of an identical pattern to that found associated with JIA.*

### **The SYCAMORE Trial**

*The Sycamore trial (ISRCTN 10065623) was a randomised controlled trial (RCT) of the clinical effectiveness, safety and cost effectiveness of Adalimumab in combination with Methotrexate for the treatment of juvenile idiopathic arthritis associated uveitis. The trial is funded by the NIHR Health Technology Assessment Programme and Arthritis Research UK. As of May 2015, recruitment was stopped on efficacy and ethical grounds.*

*A literature review was undertaken to establish the evidence base on clinically effectiveness, safety and cost-effectiveness of anti TNF alpha agents Infliximab and Adalimumab in paediatric patients with idiopathic uveitis and uveitis secondary to Juvenile Idiopathic Arthritis (JIA). It identified 7 studies (reporting clinical efficacy and/or safety) - two Infliximab Tugal-Tutkun et al. 2008, Sukumaran et al 2012); four Adalimumab (Tynjala et al 2008, Kotaniemi et al 2011, Simonini et al 2013 and Magli et al 2013) and one comparative study which included both biological agents (Simonini et al 2011). No studies on cost-effectiveness were found.*

### **Infliximab**

*The evidence supporting the use of infliximab to treat uveitis in children with JIA or idiopathic uveitis is limited (SIGN level 3; Grade D). It is based on two retrospective case series studies with small sample sizes.*

### **Adalimumab**

*The evidence supporting the use of Adalimumab in children with JIA or idiopathic uveitis is limited as it comes from 4 case series studies with small sample sizes (SIGN level 3; Grade D).*

### **Infliximab Vs. Adalimumab**

## OFFICIAL

*Evidence on the superiority of one agent over another is limited as it comes from one small comparative study (Simonini et al 2011) (SIGN level 3; Grade D).*

*There is a strong scientific rationale for the use of anti-TNF alpha agents based on what is known about the biology of uveitis through experimental models and experimental medicine (Caspi RR 2011, Dick et al 2004). Anti-TNF alpha agents have already become the standard of care in a range of inflammatory diseases with comparable biological mechanism, including severe ankylosing spondylitis and Crohn's disease (NICE TA143 and TA187).*

*The use of Infliximab and Adalimumab to treat uveitis is also supported by leading experts from Germany, the USA, France, Spain, Australia, Japan and Scotland'.*