# Clinical Commissioning Policy
# Vedolizumab for refractory ulcerative colitis in pre-pubescent children [200405P]

## Commissioning position

### Summary

Vedolizumab is not recommended to be available as a routinely commissioned treatment option for refractory ulcerative colitis in pre-pubescent children.

The policy is restricted to certain age groups as there is insufficient evidence to confirm safety and it is not recommended to be used in those age groups included in the policy.

## 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 ulcerative colitis

Ulcerative colitis (UC) is a long-term condition that mainly affects the bowel. Some people may develop symptoms that affect other body parts as well. The cause of UC is unknown and it can develop at any age, although peak incidence is between the ages of 15 and 25 years. Symptoms of active disease can include bloody diarrhoea, an urgent need to defaecate (poo) and abdominal (tummy) pain. UC is a lifelong disease that is associated with significant impact on patients' lives. It can also affect a person's social and mental wellbeing, particularly if poorly controlled.

UC has two phases which are called active and remission (inactive). There are two different treatments depending on the phase of the disease, treatment of active disease (inducing remission) or treatment aimed at maintaining remission. For this policy, refractory UC is defined as patients whose disease does not respond to the use of anti-TNF alpha, or has stopped responding to the treatment (NICE, 2013).

## About current treatment

Treatment is largely to relieve symptoms rather than cure. For mild disease, two types of therapies are generally used: aminosalicylates or steroids. For moderate to severe disease, add on therapy with stronger immunosuppressive medications such as tacrolimus or ciclosporin are used. Infliximab, a tumour necrosis factor (TNF) alpha inhibitor can be used in severe, active UC.

For children who have failed all the treatment as stated above, there is no alternative licensed therapy. These patients may be dependent on long-term steroids or require surgical interventions.

## About the new treatment

Vedolizumab is a biological medicine given through intravenous infusions. It targets a protein found on the surface of certain white blood cells involved in causing inflammation in the gut.

It is licensed for the treatment of adults with moderately to severely active UC as the fourth line treatment. Vedolizumab is not licensed for this indication in children.

## What we have decided

Vedolizumab is licensed for use in adult patients with moderately to severely active ulcerative colitis and access is defined in NICE Technology Appraisal 342 Vedolizumab for moderately to severely active ulcerative colitis. Vedolizumab is not licensed for this indication in children. As such, access for post pubescent children may be considered in line with the criteria in NHS England's Commissioning Medicines for Children in Specialised Services Policy (NHS England 170001/P, 2017). NHS England has carefully reviewed the evidence to treat refractory ulcerative colitis with vedolizumab in pre-pubescent children in this policy. We have concluded that there is not enough evidence to make the treatment available at this time.

## Committee discussion

Clinical Panel considered that the evidence base was sparse in pre-pubertal children and the evidence is supported by a NICE appraisal in adults which could be translatable in post pubescent children, hence they would be able to access treatment through the NHS England Medicines for Children policy.

Clinical Priorities Advisory Group members considered the supporting documentation. See the committee papers (link) for full details of the evidence.

### The condition

UC is a chronic, inflammatory condition which affects the bowels. The cause of UC is unknown. It can develop at any age, although peak incidence is between the ages of 15 and 25 years. UC is a lifelong disease that is associated with significant morbidity. It can also affect a person's social and psychological wellbeing, particularly if poorly controlled.

UC usually affects the rectum and the colon proximal to the rectum. Symptoms of active disease can include bloody diarrhoea, an urgent need to defaecate and abdominal pain. Typically, it has a relapsing–remitting pattern.

### Current treatments

The aim of treatment is to manage symptoms rather than cure, and active treatment of acute disease (inducing remission) should be distinguished from preventing relapse (maintaining remission) (NICE, 2013).

To induce remission, NICE recommends the following:
First line - Aminosalicylates, followed by corticosteroids.
Second line - Aminosalicylates and corticosteroids can be given in combination. Tacrolimus or ciclosporin can be considered.
Third line - Infliximab, a tumour necrosis factor (TNF) alpha inhibitor can be used for severely active UC after the failure of conventional therapy in children and young people.

**Proposed treatments**

Vedolizumab is a monoclonal antibody that reduces gastrointestinal inflammation in people with UC. Vedolizumab is a gut-selective immunosuppressive biologic that binds specifically to the α4β7 integrin. The α4β7 integrin is expressed on a subset of memory T helper lymphocytes which migrate into the gastrointestinal tract and cause inflammation that is characteristic of UC (vedolizumab, summary of product characteristics).

Vedolizumab is licensed for treating moderate to severe active UC or Crohn's disease in adults and access is defined as per NICE Technology Appraisal 342 Vedolizumab for moderately to severely active ulcerative colitis. NHS England has carefully reviewed the evidence to treat.

Vedolizumab is not licensed for this indication in children under 18 years.
Access for post pubescent children may be considered in line with the criteria in NHS England's Commissioning Medicines for Children in Specialised Services Policy (NHS England 170001/P, 2017). This policy therefore considers the use of vedolizumab to treat refractory Crohn's disease in pre-pubescent children.

## Epidemiology and needs assessment

The incidence of UC in children and young people (CYP) is increasing worldwide, ranging from 10.6 in the USA to 15 per 100,000 person years in Europe (Sýkora et al, 2018). In England the estimated incidence is 2.6 per 100,000 person-years. Population studies such as Benchimol EI et al estimate the prevalence of UC to be 10.7 per 100,000 population (Benchimol EI et al, 2017).

It is anticipated that around 30% CYP with Ulcerative Colitis will require escalation to TNF alpha inhibitor treatment, out of which, 10% will fail the treatment or not maintain a response and require vedolizumab (Ashton et al, 2018). In paediatric-onset UC, the genetic component is more dominant and recurrence within the family is more prevalent than in adults (Polito II JM et al, 1996; Griffiths AM, 2004). Childhood is a time of dynamic physical changes, bone accrual and growth along with emotional maturation. Paediatric IBD is also more often extensive and is associated with a more aggressive disease course, including a greater propensity for disease extension and early immunomodulation (Van Limbergen J, 2008; Vernier-Massouille G et al, 2008; Pigneur B et al 2010).

## Evidence summary

NHS England has concluded that there is not sufficient evidence to support a policy for the routine commissioning of this treatment for the indication for children.

An evidence review was undertaken to establish the clinical effectiveness, safety and cost-effectiveness of vedolizumab compared to standard care in the treatment of refractory ulcerative colitis in CYP of 3-18 years. However, the policy provides a commissioning position for pre-pubescent children only, as access for older children will be provided in line with the NHS England's Commissioning Medicines for Children in Specialised Services policy (NHS England 170001/P, 2017).

This evidence review includes 1 retrospective observational study (Ledder et al. 2017).

An overview of the results for clinical effectiveness and safety and tolerability can be found in the evidence summary table. The research questions for the evidence review and the key outcomes identified in the scope are discussed in this section.

The evidence presented in this review does not provide any data comparing the clinical effectiveness and safety of vedolizumab with any other treatment for the management of ulcerative colitis in children and young people.

Clinical effectiveness

This section considers whether vedolizumab is clinically effective in children and young people with refractory ulcerative colitis. Results are presented for the combined group of 41 children and young people with ulcerative colitis (33 participants) and unclassified inflammatory bowel disease (8 participants). The results for stool calprotectin and endoscopy were for a subgroup of children and young people with ulcerative colitis or inflammatory bowel disease.

Remission and clinical response:

In the retrospective observational study by Ledder et al. (2017), steroid-free remission was observed in 37% (15/41) children and young people at 14 weeks. At 22 weeks steroid-free remission was seen in 34% (14/41). Three children and young people who were in remission at week 14 were not in remission at week 22. Two children and young people who were not in remission at week 14 were in remission at week 22.

Steroid use:

Ledder et al. (2017) reported that 69% (27/39) of children and young people used corticosteroids at baseline compared with 26% (9/34) at week 14. The authors also reported a reduction in median dose of corticosteroid at week 14 compared with baseline, 12.5 mg (IQR 10 to 20 mg) at week 14 compared with 25 mg (IQR 20 to 40 mg) at baseline. No statistical analysis was reported.

Surgery:

Ledder et al. (2017) found that 15% (6/41) of children and young people needed colectomy during the follow-up period (median 24 months). Only one participant had had surgery before starting vedolizumab.

Stool calprotectin:

Stool calprotectin was measured in 20/41 children and young people at baseline and follow-up. There was a median decrease in calprotectin levels of 518 micrograms/g (IQR 202 to 2,327 mcg/g). Deep remission, defined as clinical remission with stool calprotectin <100 micrograms/g, was seen in 30% (6/20) of children and young people in whom stool calprotectin was measured.

Endoscopic assessment:

Colonoscopic assessment was carried out for 13/41 children and young people at baseline and follow-up. Two of 13 (15%) achieved mucosal healing at follow-up (defined as an ulcerative colitis endoscopic index of severity [UCEIS] score of zero).

Safety and tolerability

This section considers whether vedolizumab is safe in children and young people with refractory ulcerative colitis. Results are presented for the combined group of 64 children and young people with ulcerative colitis (n=33), Crohn’s disease (n=23) or unclassified inflammatory bowel disease (n=8).

No serious medicines-related adverse events were reported and 3 minor adverse events were reported (n=64). These were: otitis externa with periorbital oedema, intractable itch, and mild shortness of breath. Discontinuation of vedolizumab was only necessary in the young person who developed intractable itch. It is not possible to say if these adverse events were in children and young people with ulcerative colitis or Crohn's disease because the safety results were not reported separately.

Vedolizumab was discontinued in 22% (14/64) of children and young people in the follow-up period. Most discontinuations (13/14) were because of poor response. As described above one participant discontinued treatment because of intractable itch, which resolved when vedolizumab was stopped. It is not possible to say how many discontinuations were in children and young people with ulcerative colitis because the results for ulcerative colitis and Crohn's disease were not reported separately.

Adverse effect information from the summary of product characteristics (SmPC) derived from use in adults can also be used to predict the type of adverse effects likely to be seen in children. Vedolizumab is contraindicated in people with active severe infections for example, active tuberculosis. The SmPC on vedolizumab also includes special warnings and precautions for use including: potential increased risk of infection and malignancy, hypersensitivity reactions, administration of vaccines, and prior use of biologics.

Based on clinical studies and post-marketing experience with vedolizumab, the following adverse reactions are listed as being very common (incidence greater than 1 in 10): nasopharyngitis, headache and arthralgia. Other adverse effects seen commonly (incidence between 1 in 10 and 1 in 100) include upper respiratory tract infections, paraesthesia, hypertension, cough, gastrointestinal effects such as dyspepsia and nausea, as well as pyrexia, fatigue and muscle pain. For more information on these see the SmPC.

**Cost-effectiveness**
This section considers whether vedolizumab is cost effective in children and young people with refractory ulcerative colitis.

No studies were identified during literature searches (see search strategy for full details) that compared the cost-effectiveness of vedolizumab with no treatment or standard treatment in children or young people with ulcerative colitis. The study included in this evidence review does not include an outcome investigating cost-effectiveness.

## Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

## Definitions

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| Children and young people (CYP) | This policy refers to children and young people of 3-18 years. |
| Pre-pubescent children | A child or young person in the years prior to puberty, as determined by clinical judgement. |
| Colectomy | This refers to the surgical removal of all or part of the colon, also known as bowel resection. |
| Inflammatory bowel disease (IBD) | This refers to Crohn's disease and ulcerative colitis. Both causes inflammation in the bowels. |
| Immunosuppressive medications | This is a group of medication that acts by suppressing the immune system. Examples are aminosalicylates (5-aminosalicylic acid, 5-ASA), ciclosporin and tacrolimus. |
| Paediatric ulcerative colitis activity index (PUCAI) | A scoring system that evaluates UC disease activity. A score of 0 to 85 with 0 to 10: remission, 10 to 34: mild disease, 35 to 64: moderate disease and 65 and above: severe disease. |
| Refractory ulcerative colitis (UC) | This means there is high ulcerative colitis disease activity despite conventional pharmacological treatment, including inadequate response to or loss of response to TNF alpha inhibitor treatment. |
| Steroids | This includes prednisolone, methylprednisolone or intravenous hydrocortisone. |
| Stool / faecal calprotectin | This measures the level of the protein calprotectin in the stool. Increased calprotectin is a sign of inflammation in the intestine. |
| Tumour necrosis factor alpha (TNF alpha) inhibitors | This refers to a group of biological medication that blocks a pro-inflammatory molecule, TNF alpha, in the body. An example of this is infliximab. |
| Ulcerative colitis endoscopic index of severity (UCEIS) | This is a measure of endoscopic response in ulcerative colitis. It is measured on a scale of 0 to 8 and takes vascular pattern, bleeding, erosions, and ulcers into account. Endoscopic remission is defined as a UCEIS score of 0. |

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| Unclassified inflammatory bowel disease | This is a classification of inflammatory bowel disease where there are features of both ulcerative colitis and Crohn’s disease. |

## References

Ashton J, Batra A, Beattie R. 2018. Paediatric inflammatory bowel disease- brief update on current practice. Paediatrics and child health, 28(11): 507-514.

Benchimol EI et al. 2017. Trends in Epidemiology of Paediatric Inflammatory Bowel Disease in Canada: Distributed Network Analysis of Multiple Population-Based Provincial Health Administrative Database. Am J Gastroenterol 2017; 112:1120-1134.

Griffiths AM. 2004. Specificities of inflammatory bowel disease in childhood. Best Pract Res Clin Gastroenterol, 18 (3): 509-523.

Kappelman MD, Rifas-Shiman SL, Kleinman K, Ollendorf D, Bousvaros A, Grand RJ et al. 2007. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol, 5 (12): 1424-1429.

Ledder O, Assa A, Levine A et al. 2017. Vedolizumab in Paediatric Inflammatory Bowel Disease: A Retrospective Multi-Centre Experience From the Paediatric IBD Porto Group of ESPGHAN. Journal of Crohn's & colitis, 11 (10): 1230-1237.

Pigneur B, Seksik P, Viola S, Viala J, Beaugerie L, Girardet JP, et al. 2010. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. Inflamm Bowel Dis, 16 (6): 953-961.

Polito II JM, Childs B, Mellits ED, Tokayer AZ, Harris ML, Bayless TM. 1996. Crohn's disease: influence of age at diagnosis on site and clinical type of disease. Gastroenterology, 111 (3): 580-586.

Sykora J, Pomahacova R, Kreslova M, Cvalinova D, Stych P, Schwarz J. 2018. Current global trends in the incidence of paediatric-onset inflammatory bowel disease. World Journal of Gastroenterology, 24(25): 2741-2763.

Van Limbergen J, Russell RK, Drummond HE, Aldhous MC, Round NK, Nimmo ER, et al. 2008. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology, 135 (4): 1114-1122.

Vernier-Massouille G, Balde M, Salleron J, Turck D, Dupas JL, Mouterde O. 2008. Natural history of paediatric Crohn's disease: a population-based cohort study. Gastroenterology, 135 (4):1106-1113.