MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
04 March 2020

Agenda Item No	3.3
National Programme	Women & Children
Clinical Reference Group	Paediatric Medicine
URN	1862

Title
Vedolizumab for refractory ulcerative colitis in pre-pubescent children

Actions Requested	1. Support the adoption of the policy proposition
	2. Recommend its approval as an IYSD

Proposition
This is a clinical commissioning policy recommending not for routine commissioning. Ulcerative colitis (UC) is a long-term condition that mainly affects the bowel. Symptoms of active disease can include bloody diarrhoea, an urgent need to defaecate and abdominal pain. UC is a lifelong disease that is associated with significant impact on patients' lives. 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 treatments as stated above, there is no alternative licensed therapy. These patients may be dependent on long-term steroids or require surgical interventions. 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. 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).

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a not for routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

The Benefits of the Proposition		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	

8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	See below for details of adverse events
11.	Delivery of intervention	

Other health outcome measures determined by the evidence review		
No	Outcome measure	Summary from evidence review
1.	Steroid-free remission at 14 weeks	This outcome looks at the steroid-free remission rates 14 weeks after starting vedolizumab. Steroid-free remission at 14 weeks was observed in 37% (15/41) children and young people with ulcerative colitis or unclassified inflammatory bowel disease. These results suggest that vedolizumab may be effective at inducing remission at 14 weeks in some children and young people with refractory ulcerative colitis or unclassified inflammatory bowel disease. These results should be interpreted with caution because the study is small, uncontrolled and retrospective. Weaknesses in the study's design and conduct mean it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions. The results also included children with unclassified inflammatory bowel disease which may affect the applicability of the findings.
2.	Steroid-free remission at 22 weeks	This outcome looks at the steroid-free remission rates 22 weeks after starting vedolizumab. Steroid-free remission at 22 weeks was observed in 34% (14/41) children and young people. 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. These results suggest that for most children and young people whose ulcerative colitis or unclassified inflammatory bowel disease was in remission by week 14, vedolizumab was effective in maintaining remission to

		week 22. However, 3 children and young people did not remain in remission. Vedolizumab was effective in inducing remission after 22 weeks in a small number of children and young people who were not in remission by week 14. See above for limitations of the study.
3.	Steroid-free remission at last follow-up (median 24 weeks)	This outcome looks at the steroid-free remission rates at the last follow-up date. Steroid-free remission at last follow-up was observed in 39% (16/41) children and young people. These results suggest that, after a median follow-up of 24 weeks, vedolizumab was effective in maintaining remission in the same proportion of children and young people who achieved remission at week 14. The authors did not report whether these were the same participants so it is not possible to say whether those who initially achieved remission were still in remission at the last follow-up date. See above for limitations of the study.
4.	Surgical resection	This outcome looks at the number of children and young people who needed surgical resection over the follow-up period (median 24 months). Fifteen percent (6/41) children and young people needed surgical resection during the follow-up period. These results suggest that despite vedolizumab treatment, some children and young people will still need surgery. The non-comparative study design means it is not possible to say whether this is more or less than the number who would need surgery without vedolizumab treatment. See above for limitations of the study.
5.	Steroid use at 14 weeks	This outcome looks at the number of children and young people using corticosteroids 14 weeks after starting vedolizumab. Steroid use was 26% (9/34) at week 14 compared with 69% (27/39) at baseline. These results suggest that vedolizumab use reduces steroid use. No statistical analysis was reported. See above for limitations of the study. In addition, steroid use was only reported for 34 of the 41 participants at

		week 14 and the authors did not report any missing data analysis.
6.	Mucosal healing	This outcome looks at mucosal healing in a subgroup of participants. This was defined using an endoscopy score called the UCEIS. Thirteen children and young people had both baseline and follow-up colonoscopic assessment. Two of 13 (15%) achieved mucosal healing at follow-up. These results suggest that vedolizumab use led to mucosal healing in a small number of children and young people in whom this outcome was measured. See above for limitations of the study.
7.	Stool calprotectin levels	This outcome looks at stool calprotectin levels at baseline and at follow-up. Stool calprotectin was measured in 20 children and young people at baseline and follow-up. There was a median decrease in calprotectin. Deep remission, defined as clinical remission with stool calprotectin <100 micrograms/g, was achieved by 30% (6/20) of children and young people in whom stool calprotectin levels were measured. These results suggest that vedolizumab may decrease stool calprotectin levels, a marker of intestinal inflammation. See above for limitations of the study.
8.	Discontinuation of vedolizumab	This outcome looks at the number and reasons for discontinuation of vedolizumab in children and young people with ulcerative colitis, unclassified inflammatory bowel disease or Crohn's disease. Vedolizumab was discontinued in 22% (14/64) of children and young people throughout the follow-up period. The median (average) discontinuation time was 14 weeks. All but one discontinuation was because of poor response and 1 discontinuation was because of chronic itch which stopped when vedolizumab was stopped. These results suggest that the main reason for discontinuing vedolizumab was because of poor response and that vedolizumab had to be discontinued in at least a fifth of participants. See above for limitations of the study.

9.	Serious adverse events	This outcome looks at the number of serious adverse events over the follow-up period (median 24 months) in both children and young people with ulcerative colitis, unclassified inflammatory bowel disease or Crohn's disease. There were no reported serious drug related adverse events. See above for limitations of the study. In addition, it is not possible to know how the reduction in concomitant medicine use may affect this outcome and it is not possible to know what adverse events would present over a longer time period or in a larger group.
10.	Mild adverse events	This outcome looks at the number and type of non-serious adverse events over the follow-up period (median 24 months) in both children and young people with ulcerative colitis, unclassified inflammatory bowel disease or Crohn's disease. In total, 3 participants out of 64 reported non-serious adverse events. 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. The adverse events reported in the study are similar to those listed in the summary of product characteristics (SmPC) for the licensed indication in adults with infusion-related reactions and hypersensitivity reactions, such as bronchospasm, being reported and skin and subcutaneous tissue disorders being common (incidence between 1 in 10 and 1 in 100). See above for limitations of the study. In particular, it is not possible to know how concomitant medicine use may affect this outcome and it is not possible to know what adverse events would present over a longer time period.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
The Clinical Commissioning Policy proposition does not recommend vedolizumab for refractory ulcerative colitis in pre-pubescent children. This would have been an off-label use of this medicine which is licensed for 18 years and above for this indication. It is excluded from tariff.

Considerations from review by National Programme of Care
The proposal received the full support of the Women & Children Programme of Care Board on the 30/09/19. (As there were no comments received at the end of the consultation exercise, there was no need for the PoC to review its original support for the policy proposition in September 2019).