Evidence Status Report: Vedolizumab (Entyvio®) for the treatment of inflammatory bowel disease in children and young people aged 6 to 17 years: for ulcerative colitis following loss of response or non-response to anti-TNF treatment; for Crohn's disease following loss of response or non-response to anti-TNF treatment and ustekinumab **(OW24).**

Report prepared by the All Wales Therapeutics and Toxicology Centre.
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Key findings

Licence status
Vedolizumab is not licensed for the treatment of inflammatory bowel disease in children and young people (CYP) aged less than 18 years. Its use for the treatment of both ulcerative colitis following loss of response, non-response or intolerance to anti-TNF therapies; and Crohn's disease following loss of response, non-response or intolerance to anti-TNF therapies and ustekinumab is off-label for children and young people aged 6 to 17 years.

Clinical evidence
The clinical evidence for the use of vedolizumab in this setting mainly comes from a phase II, randomised, dose-ranging study and a systematic review that identified ten studies. Remission rates have been shown to be comparable if not better than those seen in the adult GEMINI studies in ulcerative colitis and Crohn's disease. However, results are subject to uncertainty given that there is a lack of placebo-controlled studies in CYP at this time.

Safety
No new safety signals have been observed for vedolizumab in this indication.

Patient factors
Vedolizumab is administered by intravenous infusion over 30 minutes. Patients should be monitored during and for two hours post-infusion for the first two infusions; one-hour monitoring post-infusion is sufficient for subsequent infusions.

Cost-effectiveness
No cost-effectiveness analyses have been undertaken in the paediatric population. The cost-effectiveness of vedolizumab has been assessed in adults: NICE TA342 (ulcerative colitis) and TA352 (Crohn's disease). Both were considered a cost-effective use of NHS resources (using the patient access scheme price).

Budget impact
Based on consultation with clinicians in Wales, 22 CYP are estimated to start treatment with vedolizumab each year at an annual cost per patient of [commercial in confidence figure removed], reducing to [commercial in confidence figure removed] after year one. The total cost in year one is [commercial in confidence figure removed], rising to [commercial in confidence figure removed] in year 3. It has been assumed that all patients receive treatment for 12 months with one quarter discontinuing treatment at year 2 and year 3. Budget impact is subject to uncertainty due to lack of longer-term discontinuation rate data. The total cost is anticipated to be lower in year 1 as half of estimated patients are currently accessing treatment through IPFR. Adverse event and monitoring costs are not included.

Impact on health and social care services
Minimal increased use of existing services.

Innovation and/or advantages
Welsh clinical experts indicate an unmet need in this population. For CYP who have failed all the current treatments in the pathway, there is no alternative licensed therapy and these patients may be dependent on steroids to control the disease. Patients are at risk of complications and repeated surgical interventions if inflammatory bowel disease is poorly controlled.

Background

Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from this treatment. Vedolizumab was therefore considered suitable for assessment though the One Wales Medicines process.

Vedolizumab is a monoclonal antibody that binds specifically to the α4β7 integrin, which is expressed on gut homing T helper lymphocytes and causes a reduction in gastrointestinal inflammation[1].

Target group

The indication under consideration is the treatment of inflammatory bowel disease in children and young people (CYP) aged 6 to 17 years: ulcerative colitis following loss of response or non-response to anti-TNF treatment; Crohn's disease following loss of response or non-response to anti-TNF treatment and ustekinumab. The age range in the indication under consideration aligns with that defined in the licensed indication for the use of anti-TNF inhibitors for ulcerative colitis and Crohn's disease in the paediatric population[2,3]. Individual patient funding request (IPFR) will remain a route of access for children under 6 years.

Marketing authorisation date: Not applicable, off-label

Vedolizumab is not licensed for the treatment of inflammatory bowel disease in CYP.

Vedolizumab is licenced for the treatment of[4]:

- Moderately to severely active ulcerative colitis in adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or an anti-TNF.
- Moderately to severely active Crohn's disease in adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or an anti-TNF.

The manufacturer of vedolizumab is planning on extending the licence to include CYP however clinical trials have been delayed due to recruitment issues. Therefore no timeframe is available for licensing in this population[5].

Dosing information

The recommended licensed dosing regimen of intravenous vedolizumab in adults is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter for both ulcerative colitis and Crohn's disease[4]. No specific guidelines exist for paediatric dosing. Most studies agree that the dose should be reduced for patients of lower weight.

Clinical background

Ulcerative colitis (UC) and Crohn's disease (CD) are the two main forms of inflammatory bowel disease (IBD). They are lifelong, chronic conditions that follow an unpredictable relapsing and remitting course and can cause significant morbidity. They can affect a person's social and psychological wellbeing, particularly if poorly controlled[6,7].

Ulcerative colitis usually affects the rectum, and a variable extent of the colon proximal to the rectum[8]. The inflammation is continuous in extent. Hereditary, infectious and immunological factors have been proposed as possible causes. It can develop at any age, but peak incidence is between the ages of 15 and 25 years. UC in CYP has several distinct features from the disease seen in adults. Common presenting symptoms of paediatric UC include diarrhoea, haematochezia, abdominal pain, and weight loss; constipation can also be an early symptom. Adults often have disease that is limited to the rectosigmoid area of the colon, but more than 80% of CYP have pancolitis. An estimated 50% of people with ulcerative colitis will have at least one relapse per year; 80% of these are mild to moderate and about 20% are severe[8]. Complications of ulcerative colitis may include haemorrhage, perforation, stricture formation (a narrowing of the intestine), abscess formation and anorectal disease. People with long-standing and extensive disease have an increased risk of bowel cancer[6].

Crohn's disease is an incurable chronic inflammatory bowel disease with 25% of patients being diagnosed under the age of 20 years[9]. Any part of the gut may be affected from the mouth to the anus. People with CD have recurrent attacks, with acute exacerbations ('flares') in between periods of remission or less active disease. The clinical features of CD are variable and are determined partly by the site of the disease. The symptoms include diarrhoea, abdominal pain and weight loss. Constitutional symptoms include malaise, lethargy, anorexia, nausea, vomiting and low-grade fever. CD can be complicated by the development of strictures, obstructions, fistulae and perianal disease. Other complications include acute dilation, perforation and massive haemorrhage, and carcinoma of the small bowel or colon[9]. It is estimated 50% of CD patients relapse and between 50% and 80% of people with CD will eventually need surgery for strictures causing symptoms of obstruction, other complications such as fistula formation, perforation or failure of medical therapy[10-12].

Delayed puberty frequently complicates the clinical course of young patients with inflammatory bowel disease, more often in Crohn's disease than ulcerative colitis. Undernutrition has been thought to be the main reason for delayed puberty in these patients[13]. However, puberty may be delayed despite a normal nutritional status. Steroid-free remission, whether clinically or endoscopically is an important treatment goal for paediatric IBD, as corticosteroids have potentially serious side effects associated with long term use including linear growth restriction, and osteopenia amongst many others[14].

Incidence/prevalence

A UK prevalence study conducted in 2020 calculated an IBD prevalence of 0.8% equating to over 500,000 people in the UK living with the condition[12]. Ulcerative colitis has a higher prevalence (0.4%) compared with Crohn's disease (0.3%) and unclassified IBD (0.07%) in the UK population[12].

Crohn's & Colitis UK estimate that around 25,000 people are diagnosed with IBD each year in the UK[12]. While incidence rates have remained stable for the last 15 years, due to population growth it is likely the number of people diagnosed with IBD in the UK will increase further[12]. IBD UK estimates there are at least 8000 CYP living with IBD in the UK[15], this would suggest there are around 400 CYP with IBD in Wales.

Current treatment options and relevant guidance

The National Institute for Health and Care Excellence (NICE) has published guidelines which covers managing ulcerative colitis in children, young people and adults (NG130) and Crohn's disease in children, young people and adults (NG129)[8,11]. Current medical approaches focus on treating active disease to address symptoms, to improve quality of life, and thereafter to maintain remission[16]. To induce remission in mild to moderate disease, first line treatment includes enteral nutrition and steroids. If this does not control the disease or the disease is severe, adding a second line therapy such as azathioprine is recommended; 5-aminosalicylate (5-ASA) drugs, budesonide, mercaptopurine and methotrexate have also been used off-label as second line treatment. Infliximab is recommended as a third line agent for people aged 6 to 17 years for CD and as a treatment option for acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate[8,11]. Anti-TNF agents are now standard of care for the treatment of IBD, however approximately 10-40% patients do not improve after anti-TNF therapy (primary non response), and 20-40% may lose response to therapy over time (second loss of response)[14]. However, unlike for adults, no alternative licensed medicinal therapies are available for CYP with IBD following loss of response or non-response to infliximab. Off-label biologics may be used and would be accessed through individual patient funding request (IPFR) in Wales. More severely affected patients may be dependent on steroids to control the disease. Patients are at risk of complications and repeated surgical interventions if the disease is poorly controlled[16].

Clinical practice recommendations for medical management of paediatric CD were published in 2020 as an evidence-based guideline by the European Crohn's and Colitis Organisation (ECCO) and the Paediatric IBD Porto group of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[17]. They recommend that in patients who fail to achieve or maintain clinical remission on anti-TNF agents, despite anti-TNF dose optimisation and immunomodulator use, ustekinumab or vedolizumab can be considered[17].

NICE recommends vedolizumab for treating moderately to severely active ulcerative colitis in adults (TA342) and for moderately to severely active Crohn's disease in adults after previous treatment (TA352)[7,9]. Access to vedolizumab for CYP in England may be considered in line with the criteria in NHS England's Commissioning Medicines for Children in Specialised Services policy apart for the treatment of refractory ulcerative colitis in pre-pubescent children[18]. In 2020, NHS England reviewed the evidence for use in this sub-population and issued a non-recommendation for the routine commissioning of this treatment option as the evidence base was considered sparse in pre-pubertal children[19].

Summary of evidence on clinical effectiveness

AWTTC conducted a literature search and identified a number of studies with the main ones of interest highlighted below. 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 IBD in CYP. There are currently four clinical trials underway in the paediatric population with estimated completion dates between in 2024 and 2030[20-23].

Efficacy

Atia et al (2022) conducted a prospective, multicentre cohort study (VEDOKIDS) which aimed to evaluate the safety, effectiveness, and dosing of vedolizumab to induce remission of IBD[24]. This paper reports on the 14-week outcomes as first analyses of a planned 3-year follow up. 142 children with a mean age of 13.6 years were enrolled, 65 (46%) children had CD, 68 (48%) had UC, and nine (6%) had unclassified IBD. The primary outcome of steroid-free and exclusive enteral nutrition-free remission at 14 weeks, based on the ITT group was met by 32 (42% [95% CI 30-54]) of 77 children with UC and 21 (32% [23-45]) of 65 children with CD. Median drug concentrations at week 14 were higher in children with UC than in those with CD (11.5 micrograms/mL [IQR 5.5-18.1] vs 5.9 micrograms/mL [IQR 3.0-12.7]; p = 0.006). In children who weighed less than 30 kg, the optimal drug concentration associated with steroid-free and exclusive enteral nutrition-free clinical remission was 7 micrograms/mL at week 14 (area under the curve 0.69 [95% CI 0.41-0.98]), corresponding to a dose of 200 mg/m^2 body surface area or 10 mg/kg[24].

Hyams et al (2022) conducted an international, phase II, randomised, dose-ranging study (HUBBLE)[25]. A total of 88 patients were enrolled weighing ≥30 kg (UC, n = 25; CD, n = 24) and <30 kg (UC, n = 19; CD, n = 21) that had a baseline mean (standard deviation) age of 13.5 (2.5) and 7.6 (3.2) years, respectively. Patients were randomised 1:1 by body weight to receive a low or high IV vedolizumab dose (≥30 kg, 150 or 300 mg; <30 kg, 100 or 200 mg) on day 1 and at weeks 2, 6 and 14. The primary endpoints evaluated were pharmacokinetic parameters and the study concluded vedolizumab serum exposure increased in an approximately dose-proportional manner for both weight groups, and achieved concentrations similar to those of adults from the previous GEMINI trials (main clinical studies in adults).
In terms of secondary endpoint, in accordance with paediatric measures, clinical response rates across weight and dose groups at week 14 ranged from 50.0 to 80.0% in patients with UC (based on a ≥20-point decrease from baseline in paediatric UC activity index [PUCAI] score) and from 45.5 to 54.5% in patients with CD (based on a ≥15-point decrease in paediatric CD activity index [PCDAI] score). Using adult and paediatric measures, in patients with UC, clinical remission rates across weight and dose groups at week 14 ranged from 20.0 to 38.5% on Mayo score index and from 30.0 to 61.5% on PUCAI. In patients with CD, clinical remission rates across weight and dose groups at week 14 ranged from 50.0 to 63.6% on CDAI and from 16.7 to 54.5% on PCDAI[25].

Fang et al (2022) conducted a systematic review that identified ten studies, comprising of 455 patients in total with CD, UC or unspecified IBD (IBD-U)[14]. The primary outcome measure of this systematic review was clinical remission; second outcome measures included: clinical response, corticosteroid-free (CS-free) clinical remission, mucosal healing, and safety. Most patients received 300 mg vedolizumab, and others received 3.6–10.3 mg/kg. The study reported 0%-35% of CD patients achieved clinical remission from short-term (6 weeks) therapy, compared to 20-64% pf patients with UC. During maintenance therapy, 17-73% of CD patients and 20-77% of UC/IBD-U patients achieved clinical remission. Approximately 33-75% of CD patients and 20-78% of UC/IBD-U patients had clinical response with quite small sample size. These findings suggested similar therapeutic response were obtained in CD and UC, which were not consistent with previously published studies in adults. Mucosal healing was found in 17-39% of CD and 15-34% of UC/IBD-U respectively[14].

Table 1 Efficacy of vedolizumab on paediatric inflammatory bowel disease[14]

IBD type	Time period	Patient numbers	Percentage rate (95% CI)	Number of studies
Clinical remission				
CD	6 weeks	19/75	25% (17-37%)	4
	14 weeks	25/85	28% (18-37%)	6
	30 weeks	12/24	52% (10-93%)	2
	1 year	43/92	46% (36-57%)	3
UC/IBD-U	6 weeks	25/70	36% (10–57%)	4
	14 weeks	52/101	48% (31–65%)	6
	30 weeks	21/31	68% (52–84%)	2
	1 year	50/112	45% (35–54%)	3
Clinical response				
CD	6 weeks	5/15	33% (9–57%)	1
	14 weeks	20/39	52% (37–67%)	4
	30 weeks	6/13	46% (19–73%)	1
	1 year	5/10	50% (19–81%)	1
UC/IBD-U	6 weeks	1/4	25% (–17–67%)	1
	14 weeks	30/44	69% (53–84%)	3
	30 weeks	18/23	78% (61–95%)	1
	1 year	15/21	71% (52–91%)	1
CS-free clinical remission				
CD	6 weeks	1/15	7% (-6–19%)	1
	14 weeks	5/37	14% (3–29%)	3
	38 weeks	0/6	0% (NA)	1
	1 year	35/78	45% (34–56%)	1
UC/IBD-U	6 weeks	0/5	0% (NA)	1
	14 weeks	17/44	39% (17–51%)	3
	38 weeks	4/5	80% (45–115%)	1
	1 year	33/81	41% (30–51%)	1

Abbreviations: CD Crohn's disease; CI confidence interval; CS corticosteroids; IBD, inflammatory bowel disease; IBD-U inflammatory bowel disease unspecified; NA not applicable; UC ulcerative disease

Clinical trials in progress

There are currently four trials ongoing in paediatric populations sponsored by Takeda:

- A Study of Vedolizumab in Children and Teenagers with Moderate to Severe Ulcerative Colitis (UC): NCT04779307: A randomized, double-blind, phase III study to evaluate the efficacy and safety of vedolizumab intravenous as maintenance therapy in paediatric subjects with moderately to severely active ulcerative colitis who achieved clinical response following open-label vedolizumab intravenous therapy[20]. This study is due to complete May 2024.
- Long-term Safety with Vedolizumab Intravenous (IV) in Paediatric Participants with Ulcerative Colitis (UC) or Crohn's Disease (CD): NCT03196427: A phase IIb, extension study to determine the long-term safety of vedolizumab IV in paediatric subjects with ulcerative colitis or Crohn's disease[23]. This study is due to complete May 2025.

- A Study of Vedolizumab in Children and Teenagers With Moderate to Severe Crohn's Disease (CD): NCT04779320: A randomized, double-blind, phase III study to evaluate the efficacy and safety of vedolizumab intravenous as maintenance therapy in paediatric subjects with moderately to severely active Crohn's disease who achieved clinical response following open-label vedolizumab intravenous therapy[21]. This study is due to complete November 2024.
- A Study of Vedolizumab in Paediatric Participants with Ulcerative Colitis (UC) or Crohn's Disease (CD): NCT05442567: A phase IIIb extension study to evaluate the long-term safety of vedolizumab intravenous in paediatric patients with ulcerative colitis or Crohn's disease[22]. This study is due to complete in February 2030.

Safety

The Summary of Product Characteristics (SmPC) for vedolizumab (Entyvio®) lists contraindications: these include active severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis and opportunistic infections such as progressive multifocal leukoencephalopathy (PML)[4].

The SmPC special warnings include details about vedolizumab's association with acute hypersensitivity reactions including anaphylaxis, recommending administration occur in a healthcare setting equipped to manage such reactions[4]. Vedolizumab selectively targets the gut and treatment should not be started in patients with active, severe infections until they are controlled; treatment should be stopped if a severe infection develops. Patients should be monitored for infections before, during and after treatment. Some integrin antagonists (including vedolizumab) have been associated with PML and patients should be monitored for any new onset or worsening of neurological signs and symptoms, and consider neurological referral if they occur. The patient is to be given a Patient Alert Card. If PML is suspected, vedolizumab treatment must be stopped and permanently discontinued if confirmed.

The SmPC lists very common (occurring in ≥ 1 in 10 people) adverse reactions as nasopharyngitis, headache and arthralgia[4].

Results from the HUBBLE study showed an overall duration of exposure to vedolizumab was a median of 99 days in both weight groups[25]. The incidence of adverse events (AEs) was similar between both disease indications in both weight groups: among patients with UC and CD, at least one AE was experienced by 80.0% and 91.3% of patients weighing ≥30 kg, respectively, and 84.2% and 90.5% of patients weighing <30 kg, respectively; most AEs were considered mild and not related to study drug. Of the 22 patients who discontinued, 15 discontinued due to AEs; of these, 13 were due to AEs of worsening UC or CD. The overall safety profile observed in this study is generally consistent with the known safety profile of vedolizumab in adults and with the common symptoms of IBD[25].

The systematic review by Fang et al identified nine studies (n = 390) reporting safety outcomes[14]. The most commonly reported adverse event was respiratory tract infection (15), nausea and vomiting (14), headache (11), fatigue (8). The phase II and III trials identified in this review showed a favourable safety profile of vedolizumab, with similar AE incidence rates compared with placebo. One study by Conrad et al. reported 38% (8/21) experienced 12 serious adverse events that required hospitalisation including dehydration/vomiting (n = 4) requiring 9 days of

hospitalisation and flare of disease (n = 3) requiring 40 days of hospitalisation, however it was unclear whether these were directly related to vedolizumab use[26].

Safety data from the VEDOKIDS study reports 32 (23%) of 142 children experienced at least one adverse event, the most common were headache (five [4%]), myalgia (four [3%]), and fever (three [2%])[24]. None of the adverse events were classified as severe, and two (1%) patients discontinued treatment due to adverse events[24].

Discussion

- Welsh clinical experts indicate there is an unmet medical need for CYPs who have failed conventional treatments in the pathway, there is no alternative licensed therapy and patients may be dependent on steroids to control the disease. Patients are at risk of complications and repeated surgical interventions if the disease is poorly controlled. For post-pubescent children, access to vedolizumab for CD and UC would be accessible in NHS England through the Medicines for Children policy in line with TA352 and TA342, respectively. There is no current agreed route of access for pre-pubescent children in NHS England. Data for this patient group is relatively sparse.
- Other licenced, NICE approved medicines for use in adults for the treatment of moderately to severely active UC are: tofacitinib (TA547), filgotinib (TA792) and ozanimod (TA828) [27-29]. There are currently two medicines being appraised by NICE for UC: mirikizumab (ID3973, date tbc) and upadacitinib (ID3953, due January 2023)[30,31]. A medicine currently being appraised by NICE for moderately to severely active CD is risankizumab (ID3986, due March 2023)[32]. These medicines are placed after the use of vedolizumab in the treatment pathways for both diseases and are also not licenced in CYP so would be used off-label. Use of these medicines in CYP would be subject to IPFR.
- There have been no studies for comparative effectiveness carried out in children. Several phase III clinical trials in the paediatric cohort are ongoing but completion dates are up to eight years away.
- There are limited safety data available. Data from published papers identified in this report suggests a similar safety profile to adults and there has been no new safety signals reported in the small cohort IBD studies, although they have relatively short follow up.
- No specific guidelines exist for paediatric dosing. Doses given in studies vary widely from 3.6 – 10 mg/kg. The study by Hyams et al demonstrated that treatment with 150 mg or 300 mg IV ustekinumab in patients weighing ≥ 30 kg and 100 mg or 200 mg IV ustekinumab in the < 30 kg group resulted in similar clinical responses at week 14 to those observed in adults. They concluded that fixed dosing appeared adequate compared with adult trials but stated that further study in the lowest weight group of the paediatric population is needed on maintenance dosing strategies[25].
- Studies included in this report have limitations including heterogeneous populations largely due to small sample size and mostly retrospective designs. There are also varying dosing regimens, differing levels of exposure to other agents and not all patients were refractory to prior treatment, including anti-TNF therapy.
- Due to the lack of placebo-controlled trials it is difficult to assess the true effectiveness of vedolizumab. Studies have been relatively short term and given the relapsing-remitting nature of IBD, its effectiveness in treating these conditions and long-term outcomes are subject to uncertainty.

- When comparing to adult data, the GEMINI studies had remission rates at 52 weeks of 36-39% in patients with Crohn's disease and 42-45% for ulcerative colitis patients[33,34]. When comparing to the data from the systematic review, these suggest broadly similar if not slightly better results in children. However, these results should be interpreted with caution given the lack of placebo-controlled trials in CYP. The GEMINI studies conducted in adults concluded that vedolizumab is more effective in treating UC than CD[33,34]. However, there is not enough data to conclude the same trend in CYP.
- The literature acknowledges the significant burden IBD has on patients' health and health-related quality of life, and on the NHS in terms of the resource use associated with the clinical manifestations of the disease[35]. The symptoms of CD and UC, and their unpredictable nature, can be detrimental to both the physical and mental health of CYP and negatively impact on educational attainment and social interaction.

Cost-effectiveness evidence

No studies on the cost-effectiveness of vedolizumab were identified for the paediatric populations. Cost-effectiveness has been assessed for vedolizumab in adult patients with CD and UC by NICE[6,9]. The relevance of these cost-effectiveness studies to the paediatric population is uncertain as variables informing the cost-effectiveness models such as disease severity definitions, disease presentation and dosing regimens are likely to be different in comparison to adults.

Crohn's disease

The company presented three models to NICE each consisting of a short-term induction phase (a decision tree) and a long-term maintenance phase (a Markov state transition model) comparing vedolizumab with conventional non-biological therapy (and infliximab and adalimumab for two of the models)[9]. NICE considered that the dosing assumptions in the first 2 models did not necessarily give an accurate estimate of costs and clinical outcomes in clinical practice and the 10-year time horizon used was not long enough to capture all associated costs and benefits. The third model, using a lifetime time horizon, focused entirely on the subgroup of patients with moderately to severely active CD in whom an anti-TNF had failed (primary and secondary failure). Because of data limitations, the company carried out an exploratory cost comparison of vedolizumab compared with other biological treatments (adalimumab and infliximab), which included scenario analyses on comparator dose escalation based on clinical expert opinion. The company provided base-case results incorporating a vedolizumab patient access scheme. The deterministic incremental cost-effectiveness ratio (ICER) for vedolizumab compared with conventional non-biological therapy was £21,620 per quality-adjusted life-year (QALY) gained (incremental costs and QALYs are confidential) and the probabilistic ICER was £27,428 per QALY gained (95% CI −7883 to 82,947). The probability of vedolizumab being cost effective compared with conventional non-biological therapy at a maximum acceptable ICER of £30,000 was 61%. The company's scenario analyses showed that continuing treatment with vedolizumab for 2 or 3 years (instead of 1 year) increased the ICER to £24,695 and £26,207 per QALY gained respectively. NICE concluded, on balance, that vedolizumab could be considered a cost-effective use of NHS resources and should be recommended for people in whom anti-TNF treatment has failed. It also concluded that when treatment duration is greater than 1 year, it would be important to identify the people who would continue to derive ongoing clinical benefit. Therefore it concluded that, in the absence of treatment failure, people receiving vedolizumab should be reassessed at 12 months and then at least annually to see if continued treatment is justified[9].

Ulcerative colitis

The company developed a model of the induction and the maintenance phases of treatment with vedolizumab and its comparators[6]. A decision tree structure was used to model the induction phase of treatment. The company's analysis was presented for 3 populations: the whole population, people who had not had anti-TNF therapy and people in whom anti-TNF treatment had failed. For the subgroup of people in whom an anti-TNF had failed, using costs based on a patient access scheme and depending on the source of utility values, the ICERs for vedolizumab compared with conventional therapy were £27,500 (Swinburn et al.), £31,900 (Woehl et al.) and £37,000 (base-case utilities) per QALY gained. On balance, NICE concluded that taking into account the uncertainty of the utility values and the costs of surgery and post-surgery care, vedolizumab for people in whom anti-TNFs had failed could be considered a cost-effective use of NHS resources if a stopping rule was applied and if vedolizumab was provided to the NHS at the price agreed in the patient access scheme. NICE has recommended therefore that vedolizumab should be given until it stops working or surgery is needed. At 12 months after the start of treatment, people should be reassessed to see whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified[6].

Budget impact

The recommended dose regimen of intravenous vedolizumab in the SmPC is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter, this was also the dosing used in the high dose cohort (≥30 kg) of the HUBBLE study[25,36]. Medicine and administration costs for this regimen are shown in Table 1. It is assumed that patients would have eight vedolizumab doses in their first year of treatment and six doses in subsequent years according to clinical need. The commercially discounted price agreed between the company and NHS Wales for vedolizumab (Entyvio®) is [commercial in confidence figure removed] for a 300 mg vial excluding VAT.

Table 1. Estimated annual costs for vedolizumab per patient in Wales

	Medicine acquisition cost*	Administration cost†	Total annual cost per patient
1st year of treatment	¶¶	¶¶	¶¶
Treatment in subsequent years	¶¶	¶¶	¶¶

*Confidential NHS Wales contract price plus VAT
† 2020-2021 National Schedule of Reference Costs: assumes 'Deliver Simple Parenteral Chemotherapy at first attendance' (HRG code SB12Z) for the first dose, followed by 'Deliver Subsequent Elements of a Chemotherapy Cycle' for subsequent doses (HRG code SB15Z)
¶¶ commercial in confidence figure removed

Table 2 shows the estimated annual acquisition costs. Based on consultation with clinical experts, 22 patients in Wales are estimated to start treatment each year with all assumed to have at least 12 months of treatment. Just over a quarter (27%) of

patients are estimated to discontinue vedolizumab per year after the initial first year of treatment.

Table 2. Estimated annual acquisition costs for vedolizumab for CYP in Wales

	Year 1	Year 2	Year 3
Number of patients	22*	38†	50¶
Total annual costs for vedolizumab treatment	¶¶	¶¶	¶¶

*Assumes all patients will have 12 months of treatment of 8 doses
†Assumes 16 patients continue from year 1 and will have 12 months of treatment (6 doses); 22 new patients will commence treatment in year 2 and will have 12 months of treatment (8 doses)
¶Assumes 28 patients continue from year 2 and will have 12 months of treatment (6 doses); 22 new patients will commence treatment in year 3 and will have 12 months of treatment (8 doses)
¶¶ commercial in confidence figure removed

Discussion

- There are no data available on discontinuation rates for CYP receiving vedolizumab. The NICE recommendation for adults state that vedolizumab should be given until it stops working or surgery is needed and, at 12 months after the start of treatment, patients should be reassessed and treatment continued only if there is clear evidence of ongoing clinical benefit. NICE also recommends to consider stopping vedolizumab if complete remission is achieved at 12 months. Therefore, budget impact calculations assume that all patients receive treatment for at least 12 months following initiation. Clinical experts anticipate that a quarter of patients will subsequently discontinue treatment in year 2 and year 3. However, it is plausible that some CYP will also discontinue treatment within 12 months of initiation, reducing the budget impact. Until further data are available, it is difficult to estimate the proportion of CYP discontinuing treatment throughout the 3-year timeframe. Hence, budget impact predictions are subject to uncertainty.
- Patient numbers do not account for those reaching the age of 18 years and moving into adult services for treatment with vedolizumab in line with NICE recommendations. However, it is reasonable to expect that the number of paediatric patients will remain relatively stable over time and, therefore, the impact this will have on estimated cost is minimal.
- Administration costs were not included except for the cost of delivering vedolizumab infusion as other associated treatments are expected to be part of standard of care for the patients in this cohort.
- Additional screening and monitoring and adverse event costs are also excluded from the budget impact.
- The budget impact is likely to be lower for year one than estimated given that half (11) of patients are already receiving treatment through IPFR.
- Children may also be eligible to enter a proposed clinical trial. This would reduce the potential uptake through the One Wales Medicines process and therefore lower the overall budget impact.

Additional factors

Prescribing unlicensed medicines

Vedolizumab is not licensed to treat this indication and is therefore prescribed ’off label’. Prescribers should consult their relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

References

1. Feagan BG, Sandborn WJ, Gasink C et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *New England Journal Medicine.* 2016;375(20):1946-1960.
2. AbbVie Ltd. Humira 40 mg/0.4 ml solution for injection in pre-filled pen. Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/7986/smpc#gref. Accessed January 2023.
3. Merck Sharp & Dohme (UK) Limited. Remicade 100mg powder for concentrate for solution for infusion. Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/3831/smpc#gref. Accessed January 2023.
4. Janssen-Cilag Ltd. STELARA®. 130 mg concentrate for solution for infusion. Summary of Product Characteristics. Feb 2022. Available at: https://www.medicines.org.uk/emc/product/4412/smpc. Accessed November 2022.
5. Takeda UK Ltd. Emailed communication from Company. Accessed November 2022.
6. National Institute for Health and Care Excellence. Technology Appraisal 342. Vedolizumab for treating moderately to severely active ulcerative colitis. June 2020. Available at: https://www.nice.org.uk/guidance/ta342. Accessed November 2022.
7. National Institute for Health and Care Excellence. Technology Appraisal 342. Vedolizumab for treating moderately to severely active ulcerative colitis. June 2015. Available at: https://www.nice.org.uk/guidance/ta342. Accessed November 2022.
8. National Institute for Health and Care Excellence. NICE Guideline,Ulcerative colitis: management NG130. May 2019. Available at: https://www.nice.org.uk/guidance/ng130. Accessed November 2022.
9. National Institute for Health and Care Excellence. Technology Appraisal 352. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. June 2015. Available at: https://www.nice.org.uk/guidance/ta352. Accessed November 2022.
10. Ghosh N, and Premchand P. A UK cost of care model for inflammatory bowel disease. *Frontline Gastroenterology.* 2015;6(3):169-174.
11. National Institute for Health and Care Excellence. NICE Guideline,Crohn's disease: management NG129. May 2019. Available at: https://www.nice.org.uk/guidance/ng129. Accessed November 2022.
12. Coeliac UK and Crohn's & Colitis UK. Epidemiology Summary: Incidence and Prevalence of IBD in the United Kingdom. Available at: https://crohnsandcolitis.org.uk/media/4e5ccomz/epidemiology-summary-final.pdf. Accessed November 2022.
13. Ballinger AB, Savage MO, and Sanderson IR. Delayed Puberty Associated with Inflammatory Bowel Disease. *Pediatric Research.* 2003;53(2):205-210.
14. Fang S, Song Y, Zhang C et al. Efficacy and safety of vedolizumab for pediatrics with inflammatory bowel disease: a systematic review. *BMC Pediatric.* 2022;22(1):175.
15. IBD UK. Paediatrics and the IBD Standards. 2019. Available at: https://www.ibduk.org/blog/2019/paediatrics-and-the-ibd-standards#:~:text=It%20is%20estimated%20at%20least%208000%20children%20and,even%20though%20their%20condition%20can%20affect%20their%20adolescence. Accessed November 2022.

16. National Health Service England. Clinical Commissioning Policy Ustekinumab for refractory Crohn's disease in pre-pubescent children [200404P]. Available at: www.england.nhs.uk/wp-content/uploads/2020/07/Ustekinumab-for-refractory-Crohns-disease-in-pre-pubescent-children-1.pdf. Accessed November 2022.
17. van Rheenen PF, Aloi M, Assa A et al. The Medical Management of Paediatric Crohn's Disease: an ECCO-ESPGHAN Guideline Update. *Journal of Crohn's and Colitis.* 2021;15(2):171-194.
18. National Health Service England. Commissioning Medicines for Children in Specialised Services Reference: NHS England: 170001/P. March 2017. Available at: www.england.nhs.uk/wp-content/uploads/2017/03/commissioning-medicines-children-specialised-services.pdf. Accessed November 2022.
19. National Health Service England. Clinical Commissioning Policy Vedolizumab for refractory ulcerative colitis in pre-pubescent children [200405P]. Available at: www.england.nhs.uk/wp-content/uploads/2020/07/Vedolizumab-for-refractory-ulcerative-colitis-in-pre-pubescent-children.pdf. Accessed November 2022.
20. Takeda. NCT04779307: A Study of Vedolizumab in Children and Teenagers With Moderate to Severe Ulcerative Colitis (UC). August 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT04779307. Accessed November 2022.
21. Takeda. NCT04779320: A Study of Vedolizumab in Children and Teenagers With Moderate to Severe Crohn's Disease (CD). August 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT04779320. Accessed August 2022.
22. Janssen Research & Development LLC. NCT02968108: A Pharmacokinetic Study of Ustekinumab in Pediatric Subjects With Moderately to Severely Active Crohn's Disease (STELARA). April 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT02968108 Accessed November 2022.
23. Takeda. NCT03196427: Long-term Safety With Vedolizumab Intravenous (IV) in Pediatric Participants With Ulcerative Colitis (UC) or Crohn's Disease (CD). May 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT03196427. Accessed November 2022.
24. Atia O, Shavit-Brunschwig Z, Mould DR et al. Outcomes, dosing, and predictors of vedolizumab treatment in children with inflammatory bowel disease (VEDOKIDS): a prospective, multicentre cohort study. *Lancet Gastroenterology Hepatology.* 2022.
25. Hyams JS, Turner D, Cohen SA et al. Pharmacokinetics, Safety and Efficacy of Intravenous Vedolizumab in Paediatric Patients with Ulcerative Colitis or Crohn's Disease: Results from the Phase 2 HUBBLE Study. *Lancet Gastroenterology & Hepatology.* 2022;16(8):1243-1254.
26. Conrad MA, Stein RE, Maxwell EC et al. Vedolizumab Therapy in Severe Pediatric Inflammatory Bowel Disease. *Inflammatory Bowel Disease.* 2016;22(10):2425-2431.
27. National Institute for Health and Care Excellence. Technology Appraisal 547. Tofacitinib for moderately to severely active ulcerative colitis. November 2018. Available at: https://www.nice.org.uk/guidance/ta547. Accessed November 2022.
28. National Institute for Health and Care Excellence. Technology Appraisal 792. Filgotinib for treating moderately to severely active ulcerative colitis. June 2022. Available at: https://www.nice.org.uk/guidance/ta792. Accessed November 2022.
29. National Institute for Health and Care Excellence. Technology Appraisal 828. Ozanimod for treating moderately to severely active ulcerative colitis. June

2022. Available at: https://www.nice.org.uk/guidance/ta828. Accessed November 2022.
30. National Institute for Health and Care Excellence. Technology Appraisal ID3953. Upadacitinib for treating moderately to severely active ulcerative colitis. June 2022. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10866. Accessed November 2022.
31. National Institute for Health and Care Excellence. Technology Appraisal ID3973. Mirikizumab for treating moderately to severely active ulcerative colitis. June 2022. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10872. Accessed November 2022.
32. National Institute for Health and Care Excellence. Technology Appraisal ID3986. Risankizumab for previously treated moderately to severely active Crohn's disease. June 2022. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10884. Accessed November 2022.
33. Sandborn WJ, Feagan BG, Rutgeerts P et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *The New England Journal of Medicine.* 2013;369(8):711-721.
34. Feagan BG, Rutgeerts P, Sands BE et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *The New England Journal of Medicine.* 2013;369(8):699-710.
35. The Royal College of Physicians. National audit of paediatric inflammatory bowel disease service provision: UK IBD audit. 2014. Available at: https://www.rcplondon.ac.uk/file/1124/download. Accessed November 2022.
36. Janssen-Cilag Ltd. STELARA®. 45 mg solution for injection (vials). Summary of Product Characteristics. Feb 2022. Available at: https://www.medicines.org.uk/emc/product/4412/smpc. Accessed November 2022.