Surrey Heartlands Integrated Care System Area Prescribing Committee (APC)
Integrated Care Partnerships (ICPs) (Surrey Downs, Guildford & Waverley, North West Surrey, East Surrey (as part of the CRESH system) & associated partner organisations.

Evidence review for Area Prescribing Committee (APC)

Medicine details	
Name, brand name	Vedolizumab (Entyvio®)
Manufacturer	Takeda Ltd
Proposed indication	Immunotherapy induced colitis
Requested by	Dr K Alexandropoulou (consultant gastroenterologist)

SUMMARY

Clinical Effectiveness

Immune checkpoint inhibitors are monoclonal antibodies which selectively antagonise checkpoint molecules (e.g. CTLA-4 or PD-1) thereby preventing their inhibitory signals to the immune system. This results in sustained immune activation and augmented anti-tumour immunity. Favourable outcomes from studies have led to approval for their use in the treatment of many cancers (including melanoma, non-small-cell lung cancer, and renal cell and urothelial cancers). However, the novel mechanism of action has led to a number of immune-related adverse effects which affect various organs including the GI tract. Colitis induced diarrhoea, is the second most common immune-related adverse event (after skin manifestations), but is the most frequent reason for the interruption of cancer treatment[1].

Patients that have severe symptoms must discontinue their life-saving treatment because of the side effects, so effective management of the colitis is key.

After ruling out infectious causes, treatments include[13]:

- loperamide (grade 1),
- oral steroids (grade 2),
- IV steroids with non-responders escalating to infliximab (grade 3)
- Proposed place in therapy for vedolizumab would be for severe colitis and diarrhoea (grade 3-4) who are refractory to infliximab.

Vedolizumab is a gut-selective monoclonal antibody targeting leukocyte integrin α4β7. It is currently licensed for the treatment of Crohn's disease and ulcerative colitis but it has a promising role in the management of immune checkpoint inhibitor-induced enterocolitis. The safety profile of vedolizumab seems favourable to systemic immunosuppression with anti-TNFα agents given that its mechanism of action is limited to lymphocyte trafficking in the GI tract. Safety data from six clinical trials showed that vedolizumab is not associated with increased risks of serious infections or malignancy[2]. The extensive research, licensing and experience for vedolizumab is not for immunotherapy-induced colitis.

See under "Evidence review" for a summary of the evidence of use of vedolizumab for the management of checkpoint inhibitor induced colitis. In all of the evidence cited the study population sizes are small reflecting the low number of immunotherapy-induced colitis patients refractory to steroids and/or infliximab.

The largest study to date[3] was a retrospective case series of 28 patients:

- 24 (86%) of 28 patients achieved sustained clinical remission

- Dosing used is different to the proposed dose in this application
- Patient population slightly different: only 9 were previously treated (unsuccessfully) with infliximab

A case study[4] (7 patients) resulted in 6/7 patients achieving steroid free remission, however the study population was small and the patients did not have any prior infliximab treatment.

A retrospective review[5] which included 34 patients treated with vedolizumab found favourable results in patients treated ≤10 days after onset of the immune-related colitis symptoms. Only 2 of the patients had been treated with prior infliximab.

2 separate case studies[6, 7] were included in the evidence review, the results of which showed a complete steroid-free remission and in one instance restarting the checkpoint inhibitor treatment. However there was no prior infliximab use in one of them (due to concerns of the systemic mechanism negating the benefit of immune checkpoint inhibitors) and in the other case study only 2 doses of vedolizumab were given.

A larger study to evaluate vedolizumab in this indication is warranted.

Vedolizumab is the most expensive options from the "IBD High Cost Immune Modulator Treatment Pathway" [6]. Other available biologic therapies in that pathway are contraindicated during active cancer therapy and for 5 years after cancer therapy. Being gut-specific, vedolizumab is less likely to reverse the therapeutic benefit of the checkpoint inhibitors and to have the additional benefit of not heightening the risk of opportunistic infection or secondary malignancies in an already vulnerable patient.

Addition of vedolizumab to the treatment options to control severe check-point inhibitor induced colitis will allow a reduction of morbidities from active disease, long term steroid therapy, and allow the patient to continue with their cancer therapy.

Sort level 2

Safety

The most commonly reported adverse reactions[7] are infections (such as nasopharyngitis, upper respiratory tract infection, bronchitis, influenza and sinusitis), headache, nausea, pyrexia, fatigue, cough, arthralgia.

Infusion related reactions (with symptoms such as dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate) have also been reported in patients treated with vedolizumab In GEMINI 1 and 2 controlled studies, 4% of intravenous vedolizumab-treated patients and 3% of placebo-treated patients experienced an adverse reaction defined by the investigator as infusion-related reaction

Infections: In GEMINI 1 and 2 controlled studies with intravenous vedolizumab, the rate of infections was 0.85 per patient-year in the vedolizumab-treated patients and 0.70 per patient-year in the placebo-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infections. Most patients continued on vedolizumab after the infection resolved.

In GEMINI 1 and 2 controlled studies with intravenous vedolizumab, the rate of

serious infections was 0.07 per patient year in vedolizumab-treated patients and 0.06 per patient year in placebo-treated patients. Over time, there was no significant increase in the rate of serious infections.

Patient factors

As vedolizumab is already being used in secondary care for its licensed indications: Systems are already in place for the procurement, supply and administration and staff are familiar with its use.

It will provide an additional option for patients with severe colitis refractory to infliximab, and high dose steroids to manage their colitis while they continue their cancer therapy with checkpoint mutation inhibitors where this is their best cancer treatment option.

A retrospective review[14] of a pharmacovigilance database highlighted the significant amount of fatal adverse effects associated with checkpoint inhibitors. The cause of death varied with which therapy was used but for example of 193 anti–CTLA-4 deaths, most were usually from colitis (135 [70%]).

Initially applied for as an IFR but the panel judged it to be a small cohort of patients.

Cost implications

The planned treatment protocol consists of the regimen licensed for Ulcerative colitis and Crohn's disease:
300mg IV x 2, then 108mg s/c every 2 weeks review at 12 months.

Successful treatment results in less hospital admissions, investigations and alternative treatments.

The costs are commercially sensitive and the same as that for treating patients for Ulcerative colitis and Crohn's disease

Even though the indications of checkpoint mutation inhibitors are expanding, the expectation is that there will be very few patients requiring this treatment. The data shows that only two patients have required infliximab, an earlier treatment, in Surrey Heartlands since it was approved in November 2017, and the overall cost is expected to be very low. Should the number of patients increase, for example to more than 10 patients in Surrey Heartlands per year, the authors would be happy to review this paper and update the APC on the evidence as this would represent greater use and would represent more experience in practice.

Relevant guidance / reviews

National guidance for the treatment of chronic immunotherapy induced colitis is not available. There is a St. Luke's pathway which was updated after the approval of infliximab for this condition at APC, describing treatment up to the point where vedolizumab is required.

- The APC approved "IBD High Cost Immune Modulator Treatment Pathway" available on Surrey PAD[8]: This is a guideline for the use/indication/commissioning of immune modulators (including vedolizumab) in Surrey and NW Sussex. It is noted that vedolizumab is the "most expensive treatment option. If used ahead of other options a risk benefit analysis should

be completed in all cases".

- (NICE TA342)[10] Vedolizumab for treating moderately to severely active ulcerative colitis (June 2015): Guidance for "the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, or lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha antagonist". It does not include colitis secondary to immunotherapy

Likely place in therapy relative to current treatments

Patients with immunotherapy induced colitis that have active cancer and in whom steroids and (first line biologic treatment with) infliximab are not effective.
The use of immunotherapy is increasing in oncology, however the type of patient in whom vedolizumab would be indicated in is a very small subset and will likely be 2-3 patients a year at most

It is being requested as a Red drug for treatment by gastroenterologists, where the subcutaneous injection is to be supplied by home care after the intravenous loading doses.

Recommendation to APC

The APC is asked to approve this treatment as a RED indication for patients with stage 3 to 4, chronic immunotherapy induced colitis refractory to steroids and infliximab
The APC is asked to approve this treatment:

- Despite the reduced evidence base reflecting the very small number of patients who are likely to be affected by this condition which would limit their cancer treatment.
- Recognising that, although this is an unlicensed indication, the drug is well known to gastroenterologists and
- The authors recognise that the number of cases could increase because of:
  - An increased use of checkpoint inhibitors,
  - New checkpoint inhibitors with a different adverse effect profile or
  - Additive effect from a combination of checkpoint inhibitors.

If the number of patients increases, it is expected that there will be more accompanying evidence and the authors are willing to review the evidence and report back to the APC.

Medicine details	
Name and brand name	Vedolizumab (Entyvio®)
Licensed indication, formulation and usual dosage	Entyvio® is indicated for the treatment of adult patients with moderately to severely active Crohn's disease/Ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.
Summary of mechanism of	*Information below is from the SPC[9]:*

action, and relevant pharmacokinetics	Vedolizumab is a gut-selective immunosuppressive biologic. It is a humanised monoclonal antibody that binds specifically to the $\alpha_4\beta_7$ integrin, which is preferentially expressed on gut homing T helper lymphocytes. By binding to $\alpha_4\beta_7$ on certain lymphocytes, vedolizumab inhibits adhesion of these cells to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), but not to vascular cell adhesion molecule-1 (VCAM-1). MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T lymphocytes to tissues within the gastrointestinal tract. Vedolizumab does not bind to, nor inhibit function of, the $\alpha_4\beta_1$ and $\alpha_E\beta_7$ integrins. The $\alpha_4\beta_7$ integrin is expressed on a discrete subset of memory T helper lymphocytes which preferentially migrate into the gastrointestinal (GI) tract and cause inflammation that is characteristic of ulcerative colitis and Crohn's disease, both of which are chronic inflammatory immunologically mediated conditions of the GI tract. **Pharmacokinetics:** Population pharmacokinetic analyses indicate that the distribution volume of vedolizumab is approximately 5 litres. Not expected to bind to plasma proteins and does not cross the blood-brain-barrier. Population pharmacokinetic analyses indicate that vedolizumab has a total body clearance of approximately 0.169 L/day and a serum half-life of 24 days. Population pharmacokinetic analyses suggest that while low albumin, higher body weight and prior treatment with anti-TNF drugs may increase vedolizumab clearance, the magnitude of their effects is not considered to be clinically relevant. Vedolizumab exhibited linear pharmacokinetics at serum concentrations greater than 1 mcg/mL.
Important drug interactions	No interaction studies performed. Live vaccines, in particular live oral vaccines, should be used with caution concurrently with vedolizumab
Monitoring requirements	Monitoring for efficacy: symptoms, infection markers. Monitoring for toxicity: - Hypersensitivity/anaphylaxis during and after administration. - Development of opportunistic infections - New onset/worsening neurological signs and symptoms (progressive multifocal leukoencephalopathy).
Prescribing considerations	• Likely traffic light status (see attached guidelines) Red

	Colour classification guidelines
Other considerations	Already in use for licensed indication- staff are already trained on administration etc. St Lukes cancer alliance treatment pathway may need to be updated if this application is approved. Treatment will be reviewed via biologics MDT

Potential patient group (if appropriate to include)	
Brief description of disease	Patients that have received immune checkpoint inhibitor treatment for cancer (currently NHSE funding includes melanoma, NSCLC, renal cell carcinoma, Head & Neck cancer, and Hodgkin's disease) and have steroid and infliximab refractory colitis. Diarrhoea is the second most common immune-related adverse event (after skin manifestations), but is the most frequent reason for the interruption or permanent discontinuation of immune checkpoint inhibitor therapy. This risk is affected by the type of immunotherapy regimen, with diarrhoea occurring most frequently in patients treated with anti-CTLA-4 antibodies, and is more common in anti-CTLA-4 and anti-PD-1 combination therapy than with anti-PD-1 monotherapy. Immunotherapy induced colitis has the hallmarks of inflammatory colitis, and some authors argue that immunotherapy may unmask underlying primary inflammatory colitis.
Potential patient numbers per 100,000	Infliximab was approved for this indication in November 2017. Since then 2 doses have been used in Surrey Hearthlands. There is now the first patient for whom vedolizumab has been indicated, and therefore the numbers are expected to be very small. Estimated at 2-3 per year or equivalent to around 0.3 cases per 100,000
Outcomes required	The expected treatment benefits consist of Control/Resolution of colitis. Reduced morbidity from active disease and long term steroid therapy. Improved overall wellbeing to enable completion of cancer therapy.

Summary of current treatment pathway
Taken from: ➢ British Society of Gastroenterology endorsed guidance for the management of immune checkpoint inhibitor-induced enterocolitis (The Lancet)[1] ➢ The guidelines for Management of Immunotherapy-Related Adverse Events

(St Lukes Cancer Alliance website)[11]

For patients presenting with immune checkpoint inhibitor-enterocolitis:

- Immunotherapy discontinuation (If Grade 4 colitis)
- Early administration of oral corticosteroids (mild disease) or IV corticosteroids (moderate to severe disease)
- Absence of response to oral steroids- escalate to IV
- If receiving high dose IV steroids, biologics work up (pre screening) should be carried out
- If no response to high dose IV steroids (after 3 days) or mucosal ulceration/extensive colitis- initiate infliximab (stat and repeat dose after 2 weeks if required)
- If not responding to infliximab- we propose that vedolizumab should be trialled.

Evidence review

1) The largest study to date is a retrospective case series[3] of 28 patients with biopsy-proven immune checkpoint inhibitor- induced enterocolitis. All patients were refractory to corticosteroids, and nine (32%) patients did not respond to infliximab therapy.
    - Primary outcome: the duration from first vedolizumab infusion to improvement of clinical symptoms to grade 1 or below as one of the outcomes. Clinical remission of symptoms was defined as sustained resolution of diarrhoea to grade 1 or lower after vedolizumab therapy.
    - 9 of the 28 patients received infliximab in addition to corticosteroid therapy. Five of these nine patients had also undergone an unsuccessful trial of mesalamine in addition to corticosteroid therapy. The median number of infliximab infusions was two. Infliximab therapy was deemed to have failed in all patients owing to persistent or recurrent symptoms after 1 month of infliximab therapy.
    - Vedolizumab was given following the same standard as when used to treat IBD, at 300 mg for each infusion via the standardized IBD infusion schedule. Patients received a median of three doses of vedolizumab (but we are proposing 2 doses of 300mg before changing to maintenance therapy of 108mg subcutaneously every 2 weeks)
    - One patient developed a skin rash after vedolizumab infusion, which was thought to be caused by drug allergy, and that patient was switched to infliximab therapy. Additionally, one patient developed diffuse joint pain after one dose of vedolizumab, which led to discontinuation of vedolizumab, but the patient achieved clinical remission of colitis.
    - With a standard inflammatory bowel disease induction regimen, 24 (86%) of 28 patients achieved sustained clinical remission after a median of three infusions. At 6 months' follow-up, seven (54%) of 13 patients who had abnormal endoscopic findings initially, achieved endoscopic remission. Similar to the IBD experience with vedolizumab, patients who had never been given infliximab were more likely to achieve clinical remission with vedolizumab than patients previously treated with infliximab (95% vs 67%). Results indicate clinical remission more likely with vedolizumab when infliximab has not been given previously. However, this is weak evidence and the lack of comparative

studies as well as the significance price difference means that vedolizumab as the first line biologic agent is not viable currently

2) Berggvist et al[4]:
   - Case series of 7 patients with metastatic melanoma or lung cancer, treated with vedolizumab off-label for ipilimumab- or nivolumab-induced enterocolitis, from June 2014 through October 2016.
   - Patients initially received corticosteroids but were steroid-dependent and/or partially refractory.
   - Following vedolizumab therapy, six out of seven patients experienced steroid-free enterocolitis remission, with normalized faecal calprotectin. This was achieved after a median of 56 days from starting vedolizumab, without any vedolizumab-related side-effects noted. The patient in whom vedolizumab was not successful, due to active ulcerative colitis, received vedolizumab prophylactically.

3) Abu-Sbeih et al[5]:

Note: immune-mediated colitis (IMC), selective immunosuppressive therapy (SIT)

   - Retrospective review of 1459 patients who received immune checkpoint inhibitors, 179 developed IMC of any grade; 84 of these 179 patients received SIT
   - Compared with patients who received SIT > 10 days after IMC onset, patients who received early SIT (≤10 days) required fewer hospitalizations ($P = 0.03$), experienced steroid taper failure less frequently ($P = 0.03$), had fewer steroid tapering attempts ($P < 0.01$), had a shorter course of steroid treatment ($P = 0.09$), and had a shorter duration of symptoms ($P < 0.01$). Patients who received one or two infusions of SIT achieved histologic remission less frequently ($P = 0.09$) and had higher faecal calprotectin levels after SIT ($P = 0.01$) compared with patients who received three or more infusions.
   - Conclusion: SIT should be introduced early in the disease course of IMC instead of waiting until failure of steroid therapy or steroid taper

4) J.Meserve et al[12]:
   - Systematic literature review (July 2020): Looked at 12 studies reporting the impact of immune checkpoint inhibitors in 193 patients with inflammatory bowel disease. Outcomes: relapse of inflammatory bowel disease, need for corticosteroids and/or biologics to manage IBD relapse, and discontinuation of immune checkpoint inhibitors.
   - Biologic therapy for management of gastrointestinal irAEs is recommended in patients with failure of corticosteroids. In our review, roughly half the patients with flare of pre-existing IBD who received immune checkpoint inhibitors and were steroid-refractory, requiring escalation to biologic therapy. Infliximab was the most commonly used biologic agent. In two studies, vedolizumab was also used though effectiveness was not stratified by type of biologic agent. In a cohort of immune checkpoint inhibitor-induced gastrointestinal irAEs who failed corticosteroids (n = 19) and infliximab (n = 9), Vedolizumab's gut-tropic mechanism of action without systemic immunosuppression in patients

with advanced cancers make it a potentially attractive option for patients who experience IBD relapse with immune checkpoint inhibitors after failure of corticosteroids and/or infliximab.

5) Case study (69 year old man)[6]
   - Vedolizumab successfully treated steroid-dependent immune-mediated colitis due to ipilimumab, resulting in a sustained complete steroid-free remission
   - Not treated with infliximab (vedolizumab first line) as infliximab has a systemic effect, it may add to the risk of infection in patients already receiving high-dose corticosteroid. Also concern about infliximab's systemic mechanism of action suppressing T-cell activation and perhaps negating the benefit of immune checkpoint inhibitors.

6) Case study (62 year old woman)[7]
   - Following ipilimumab and nivolumab treatment
   - Received 5 mg/kg infliximab at week 0, 2, 6, and 14 (but still steroid dependent)
   - Developed CVC–induced methicillin-sensitive *Staphylococcus aureus* bacteremia after her first infliximab infusion. After TDM: classified as a primary non-responder to infliximab.
   - Three days after the first dose of 300 mg IV vedolizumab, the patient had a dramatic symptomatic improvement. After the second dose of 300 mg IV vedolizumab at week 2, she had 2 formed bowel movements per day, and prednisone was tapered down to 10 mg/day; without additional doses of vedolizumab, she was able to resume nivolumab and remained diarrhea-free at her 6-month follow-up.

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	None available
Recommendations from national / regional decision making groups	None available
Stakeholder views	Gastroenterology consultants who may be involved in the treatment of immunotherapy-induced colitis would like access to vedolizumab for the specified indication on the rare occasion that it is required. Patient views not sought as very low usage- not applicable but will given all the information required for informed consent before being given this unlicensed medicine
CCG priorities	Not considered

Health economic considerations	
Cost per year per patient	Include annual cost per patient, and population cost per 100,000 people

	300mg IV twice and then 108mg s/c every 2 weeks. Using BNF pricing= £2050 x 2 = £4100 24 x £512.50 = £12300 £4100 + £12300 = £16400/patient/year (list price before NHS discount)
Alternative treatments cost per patient per year	This has not been calculated
Other financial considerations (if relevant)	Reduction of inpatient admissions for acute colitis and reduced need for surgical interventions.
Health economic data (if available)	Not available

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Include references written in Vancouver style

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Added post-consultation comments:

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nil
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VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
v.1	*10/08/2021*	*CJoanes*		*Out for consultation*
v.2				