AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Vedolizumab (Entyvio®) for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and/or other immunosuppressant drugs like infliximab, or when infliximab is unsuitable (OW22)

February 2023

ONE WALES INTERIM DECISION

Vedolizumab (Entyvio®) for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and/or other immunosuppressant drugs like infliximab, or when infliximab is unsuitable

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been endorsed by health board Chief Executives.

Using the agreed starting and stopping criteria, vedolizumab (Entyvio®) can be made available within NHS Wales for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and infliximab, or when infliximab is unsuitable.

The risks and benefits of the off-label use of vedolizumab (Entyvio®) for this indication should be clearly stated and discussed with the patient to allow informed consent.

Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

Starting and stopping criteria for infliximab for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and/or other immunosuppressant drugs like infliximab, or when infliximab is unsuitable

Developed in collaboration with Velindre Cancer Centre.

Starting criteria:

Patients with severe or life threatening (grade 3/4) diarrhoea or colitis with **any** of the following symptoms/features present:

- 7 or more stools/day over baseline
- Severe abdominal pain
- Fever
- Dehydration
- Blood or mucus in stool
- Flexible sigmoidoscopy indicates presence of high-risk endoscopic features, mucosal ulceration or extensive colitis
- Colostomy patients

And symptoms are persisting for three or more days despite high dose methylprednisolone (1-2mg/kg/day)

And symptoms are persisting despite infliximab 5mg/kg given for up to three doses, or where infliximab is deemed unsuitable (due to high tumour burden, patient age, patient frailty or a contra-indication to the use of infliximab - see One Wales guidance for infliximab).

Screening

Prior to commencing vedolizumab, pre-screening should be undertaken to exclude:

- Active or latent tuberculosis
- Hepatitis virus or HIV
- Current acute infections (viral, bacterial, fungal or parasitic)
- Gastrointestinal perforation

Dose

The recommended treatment dose regimen for vedolizumab is 300 mg given intravenously on weeks zero, two and six. Not all cases will require three doses, treatment can be stopped before completing the course if there is sufficient response after the first or second dose. Standard treatment though is 3 doses.

Outcome data, including the number of doses used should be collected to inform future policy changes.

Only one course (three doses) may be issued in accordance with this advice. Requests for repeat courses or continuing treatment beyond three doses should be explored through funding mechanisms such as the individual patient funding request process.

Monitoring

- Infusion-related reactions including anaphylactic shock
- Injection site for signs of phlebitis
- Any new onset or worsening of neurological signs and symptoms
- Daily stool chart
- Daily bloods e.g., FBC, U&E, LFTs, CRP
- Blood cultures if pyrexial
- National Early Warning Score (NEWS) assessment
- Fluid balance
- Faecal calprotectin

Prescribers should consult the relevant Summary of Product Characteristics (SmPC) for any additional monitoring requirements and potential adverse effects. There is a potential risk of progressive multifocal leukoencephalopathy (PML). Patients should receive a patient information leaflet and a Patient Alert Card.

Stopping criteria:

- Treatment failure, progression of symptoms or minimal response
- Toxicity to treatment (that cannot or does not respond to temporary treatment interruption)
- Patient request

Failure to respond to vedolizumab:

If there is no response or symptoms are deteriorating after one, two or three doses of vedolizumab then seek advice from Gastroenterology and/or consultant leads from the Immunotherapy toxicity service.

Reference:

Merck Sharp Dohme. Vedolizumab (Entyvio) 300 mg powder for concentrate for solution for infusion. Available at: https://www.medicines.org.uk/emc/product/5442/smpc. Accessed 14 December 2022

One Wales Medicines Assessment Group summary of decision rationale

Medicine: **vedolizumab**
Indication: **for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and/or other immunosuppressant drugs like infliximab, or when infliximab is unsuitable**
Meeting date: **28th November 2022**

Criteria	OWMAG opinion
Clinical effectiveness	OWMAG note that although diarrhoea and colitis are considered separately within the National Cancer Institute's Common Terminology Criteria for Adverse Events tool, for the purposes of this assessment the British Socity of Gastroenterology definition of ICI induced enterocolitis should be used. OWMAG note that the main clinical effectiveness evidence is from a number of retrospective studies and two network meta-analyses (NMAs). The data are limited but suggests treatment efficacy after infliximab failure and, when compared to infliximab, an association with lower hospitalisation and recurrent infection rates. When reported, the group note that vedolizumab dosage used was consistent with that recommended in national and international guidelines. Both NMAs found vedolizumab to be relatively effective in terms of disease response. The limited yet positive reports from experts who had used vedolizumab to treat patients were noted. OWMAG considers that the evidence provided demonstrated clinical effectiveness.
Cost-effectiveness	No cost-effectiveness evidence was presented. OWMAG acknowledged that that their may be additional cost savings for vedolizumab in terms of the potential for earlier discharge from hospital and a reduction in the number of future hospitilisations as well as less need for more costly interventions such as surgery. There were potential health related benefits for patients in terms of reducing the amount and length of steroid courses (and the side effects associated with steroid use), reducing the need for invasive surgery and improving symptom control, thereby improving quality of life. OWMAG considered that the economic evidence presented suggested that this treatment be placed after infliximab at this time.
Budget impact	OWMAG considers the clinical estimate of patient numbers reported to be reasonably accurate. The group acknowledges that budget impact estimates are subject to uncertainty due to individual patient circumstances regarding dosage frequency

	and the finite timeframe within which patients would receive treatment. The group note that mortality rates and additional screening and monitoring for bacterial, viral and fungal infections and adverse event costs have not been included in the budget impact. OWMAG consider that the budget impact of vedolizumab may be lower due to costs saved with a reduction in length and number of hospital stays. OWMAG acknowledge that a proportion of patients with ICI induced enterocolitis in Wales are already receiving vedolizumab through local agreement routes. Also as ICI usage grows, it is acknowledged that patient numbers are anticipated to double over the coming years, resulting in additional budgetary impact in Wales. OWMAG consider that the base case provided in the report is a reasonable estimate of the associated cost to NHS Wales.
Other factors	As usage of ICIs increases, incidence of immune-related adverse events such as enterocolitis will also increase. OWMAG considers that ICI treatment for malignancies will not be a viable option if clinicians are unable to treat this associated toxicity. OWMAG consider the effect of vedolizumab on the quality of life of the pateints to be positive, in particular with respect to the reduction in hospital stays and improvement or resolution of debilitating symptoms. OWMAG noted the concerns of patients in terms of being able to go out due to worries over access to toilets and risk of incontinence. Patients may feel unable to go out and this can be isolating. OWMAG acknowledge the need for enterocolitis to be treated promptly, currently patients are often transferred to gastroenterology services before receiving treatment with a potential for delay in treatment. A One Wales decision will allow for patients to be treated within oncology services. As vedolizumab targets the gut and has no identified systemic immunosuppressive activity, clinicians suggest this may offer potential benefits over infliximab, especially for patients with high disease burden and fewer cancer treatment options. There are no licensed alternative treatment options routinely available. Vedolizumab may reduce the need for more invasive surgical interventions for this condition.
Final recommendation	OWMAG recommends the use of vedolizumab (Entyvio®) for the treatment of immune checkpoint inhibitor induced grade 3-4

	enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and infliximab, or when infliximab is unsuitable This recommendation is subject to the development of appropriate start/stop criteria including defining patients unsuitable for treatment with infliximab .
Summary of rationale	There is some limited clinical evidence to support vedolizumab as an effective treatment option for treatment of ICI induced enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and/or other immunosuppressant drugs like infliximab, or when infliximab is unsuitable. There are no licensed alternative treatment options and without access to vedolizumab for this indication ICI treatment for malignancies will not be a viable option. A proportion of the patient population in Wales are already receiving this treatment via local agreement routes, supporting the use on an All Wales basis would ensure equity of access. The review after 12 months will provide more clarity around patient numbers and the number of doses of vedolizumab administered.

The information in this document is intended to help healthcare providers make an informed decision. This document should not be used as a substitute for professional medical advice. Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the One Wales policy and this found there to be a positive impact. Key actions have been identified and these can be found in the One Wales Policy EHIA document.

Information presented in this document can be reproduced using the following citation: One Wales Interim Decision. Vedolizumab (Entyvio®) for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and/or other immunosuppressant drugs like infliximab, or when infliximab is unsuitable (OW22) 2023.