One Wales Medicine Assessment Group summary of decision rationale
Medicine: **infliximab**
Indication: **Reassessment of OW21 to extend the indication to include:**

- **patients with ICI-induced grade 2 enterocolitis when symptoms have not responded to first-line immunosuppression with corticosteroids, as an alternative to vedolizumab**
- **patients with grade 2–4 enterocolitis who are corticosteroid-dependent requiring multiple challenges with corticosteroids**
- **dose escalation to 10 mg/kg when there has been an inadequate response to standard 5 mg/kg dosing in patients with grade 2-4 enterocolitis.**

Meeting date: **19 August 2024**

Criteria	OWMAG opinion
Clinical effectiveness and safety	OWMAG note that the current One Wales decision (OW21) recommends infliximab to treat ICI-induced enterocolitis grade 3–4 that had not responded to corticosteroids. This reassessment is in response to 12-month review of OW21 which identified change to European Society for Medical Oncology (ESMO) guidelines for treating ICI-induced enterocolitis. The One Wales Medicines Assessment Group (OWMAG) proposed that, in accordance with the new treatment guidelines, infliximab should be reassessed for the broader indication of treating ICI-induced grade 2–4 enterocolitis that had not responded to corticosteroid treatment and to consider the use of a higher (10 mg/kg) dose of infliximab. This proposal was supported by Welsh clinicians who also requested that patients with grade 2-4 disease whose condition is settling and re-flaring and requires multiple steroid escalations be included in the expanded indication being considered. OWMAG note that there is limited new clinical effectiveness evidence to that already presented and considered as part of the original assessment and the 12-month review. New evidence presented that includes grade 2 enterocolitis and dose escalation is limited and consists of 3 retrospective studies, interim results of an ongoing clinical trial and a case series investigating 10 mg/kg infliximab for refractory enterocolitis. For the treatment of grade 2 enterocolitis, the group notes that infliximab dosage used (when reported) was consistent with the 5 mg/kg dose recommended in national and international guidelines while dosing schedule frequency varied with generally no more than three doses received. However, results were generally reported for the mixed colitis group (grade 1-4) with no stratification by grade. All studies showed a clinical benefit in terms of enterocolitis symptom improvement and partial or complete response to

	treatment with infliximab and reflected the results of previous studies. OWMAG note that for the dose escalation study, 50% of patients with severe enterocolitis who had not responded to the standard 5 mg/kg dose of infliximab had a clinical response to the 10 mg/kg dose although the number of patients included in the study was small. OWMAG note the evidence provided by clinical experts, both in the ESR and at the meeting, who reported positive clinical outcomes for patients that had been treated with infliximab. Clinicians highlighted that the majority of patients with grade 2 enterocolitis unresponsive to steroid treatment progress to grade 3. At this point, such patients will become eligible for treatment with infliximab or vedolizumab via OW21 and OW22. Allowing use of infliximab earlier in the pathway prevents the worsening of symptoms and lessens steroid burden by allowing rapid steroid weaning. Clinicians also highlight that 90% of patients with grade 2 enterocolitis who are successfully treated with either infliximab or vedolizumab are able to resume their cancer-treatment with ICIs; this compares to 25- 33% of patients with grade 3 enterocolitis. The detrimental impact of the prolonged use of high dose corticosteroids was also discussed; these can result in a range of serious adverse events including some that are irreversible, prevention or delay of cancer-related treatments or surgery and a decrease in quality of life. Clinicians also highlight that some patients with enterocolitis are steroid-dependent and require multiple treatment courses with steroids for relapses. They note concerns regarding the increase risk of steroid-related adverse events due to repeated exposure and would welcome the option to use infliximab for these patients to prevent future relapses and lessen steroid burden. OWMAG note that no new safety signals have been observed for the use of infliximab to treat ICI-induced enterocolitis. OWMAG considers that the evidence provided demonstrated clinical effectiveness.
Cost-effectiveness	There is no published cost-effectiveness evidence available for infliximab for the extended indication. OWMAG considered the cost-consequence analysis, threshold analysis and scenario analyses presented. The group acknowledged the limited scope of the analyses in terms of capturing all costs and effects, in particular longer term costs and effects.

	Clinicians shared their experiences in treating this patient group, suggesting that: • the majority of patients not responding to corticosteroids would progress to grade 3 • if grade 2 patients are treated successfully, then approximately 90% can be rechallenged with ICI compared with 25% or 33% of patients who experience grade 3 ICI-induced enterocolitis • Grade 3 patients tend to be treated as day-cases rather than in-patients • Monitoring is intensive for patients with steroid burden • ICI-induced enterocolitis is very different to ulcerative colitis (UC), and that unlike UC, it is reversible with limited treatment options. Therefore, they would expect that the likely expected gain in benefits would be higher for patients with ICI-induced enterocolitis. On consideration of these factors OWMAG consider it is likely that the cost of infliximab for these additional patient groups is a reasonable use of NHS resources.
Budget impact	OWMAG consider the clinical estimate of patient numbers reported to be reasonable. The group note that the majority of eligible patients with ICI-induced enterocolitis in Wales can already receive infliximab through the existing OW21 recommendation for grade 3–4 colitis. The group also note that, as the first review of OW21 indicated the actual number of patients receiving infliximab was lower to that predicted in the original assessment, the estimated population who will receive infliximab has been revised down even after accounting for the additional patients covered by the expanded indication. This has resulted in a lower budget impact range than that calculated for the original assessment. Based on outcome data provided by Welsh clinicians for patients treated with infliximab for grade 3 enterocolitis, OWMAG note that it's likely that the majority of patients will receive three doses and so the yearly budget impact is likely to be at the higher end of the estimate. 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 acknowledge that a proportion of patients with grade 2 ICI induced enterocolitis in Wales are already

	receiving infliximab through local agreement routes. Also, as ICI usage grows, it is acknowledged that patient numbers are anticipated to increase over the coming years, resulting in additional budgetary impact in Wales. This will be monitored as part of the review process. OWMAG consider that the base case provided in the report is a reasonable estimate of the associated cost to NHS Wales.
Other factors	OWMAG acknowledges that although grade 2 colitis is milder than grade 3, it can still significantly impact patients' quality of life. This may include malnutrition, poor sleep, inability to work, lethargy and chronic dehydration. In addition, OWMAG also acknowledge that long term and/or high dose steroid exposure is associated with increased risk of a wide range of adverse effects including infections, fractures, high blood sugar, cardiovascular and cerebrovascular events and that there are clinical, cost and quality of life benefits in reducing steroid burden and repeated exposure to corticosteroids. It was noted that many patients are elderly and these effects may be more severe. The use of infliximab may help a rapid wean from steroids. OWMAG also considers that earlier intervention and resolution of enterocolitis enables resumption of cancer treatment with ICIs for the majority of patients which offers an increased possibility of durable outcomes. It was noted that for patients with a low albumin level, the higher dose of infliximab may be required to achieve an adequate response. There are no licensed alternative treatment options routinely available.
Final recommendation	OWMAG recommends that the existing recommendation for the use of off-label infliximab for the treatment of ICI-induced grade 3-4 enterocolitis unresponsive to corticosteroids and outlined in OW21 be updated to include the expanded indication considered in this reassessment. Therefore, the updated recommendation is as follows: Infliximab can be made available within NHS Wales: • for the treatment of immune checkpoint inhibitor (ICI) induced grade 2-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids.

	• for the treatment of grade 2–4 enterocolitis in patients who are corticosteroid-dependent requiring multiple challenges with corticosteroids • for the treatment of grade 2-4 enterocolitis in patients requiring dose escalation to 10 mg/kg when there has been an inadequate response to standard 5 mg/kg dosing. This recommendation is subject to the development of appropriate start/stop criteria.
Summary of rationale	There is some limited evidence to support the use of infliximab as a clinically effective option for the treatment of ICI induced grade 2-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids, and for patients who are steroid-dependent and require multiple treatment courses with steroids for relapses and for dose escalation to 10 mg/kg when there has been an inadequate response to standard 5 mg/kg dosing. There are no licensed alternative treatment options and recent updates to international guidelines recommend the use of infliximab for these additional populations. Allowing the use of infliximab earlier in the pathway may prevent the worsening of symptoms, lessen steroid burden by allowing rapid steroid weaning, allow resumption of ICIs to treat the patient's cancer and maintain or improve their quality of life. A proportion of the extended patient population in Wales is already receiving this treatment via local agreement routes, supporting the extension 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 infliximab administered.