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Off-label ustekinumab regimens for inflammatory bowel disease including Crohn's disease and ulcerative colitis

Recommendation	Escalation of ustekinumab for Crohn's disease or ulcerative colitis beyond the maximum dose and frequency recommended by manufacturer is not recommended for routine commissioning due to limited evidence base for clinical efficacy and safety, lack of data on cost-effectiveness and significant cost.
Background	Ustekinumab is a human monoclonal antibody used to treat autoimmune conditions including inflammatory bowel disease (IBD). It is one of the biologic treatments recommended by NICE and commissioned under the GMMMG High Cost Drugs IBD pathway to treat Crohn's disease and ulcerative colitis.[1] According to NICE TA456, ustekinumab is recommended within its marketing authorisation as an option for adults with moderately to severely active Crohn's disease and who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or anti-tumour necrosis factor (TNF) or have medical contraindications to such therapies.[2] NICE TA633 recommends using ustekinumab for moderate to severe ulcerative colitis similarly unresponsive to anti-TNF or where these agents are not suitable.[3] To initiate treatment ustekinumab is given intravenously (induction) following which subcutaneous injection of 90mg is given at 8 weeks and thereafter 12 weekly (maintenance) dosing is recommended as by the manufacturer. Maintenance dosing may be increased to every 8 weeks for patients who lose response on dosing every 12 weeks. If no evidence of therapeutic benefit is seen at week 16 the treatment should be discontinued.[4] There has been a growing number of requests from clinicians to allow some patients who have lost response to 90mg every 8 weeks to reduce the dosing interval to every 4 weeks. This is an off-label use of ustekinumab as well as outside of NICE's cost-effectiveness assessment. Although there is emerging evidence for clinical efficacy and safety, for use of ustekinumab escalation outside of product's marketing authorisation in Crohn's disease and to a lesser extent in ulcerative colitis, due to the significant cost impact of such intervention has only been considered through the individual funding route.

Efficacy and safety	The evidence for use of ustekinumab in IBD at intervals shorter than specified in marketing authorisation is limited in quantity and of moderate grade (mainly level 2, retrospective, observational cohort studies). Common limitations include small sample size, limited follow up periods, heterogeneity, lack of control group and retrospective approach. Some larger trials were designed to investigate treatment of patients with Crohn's disease pending marketing authorisation for this indication, where experience with dose escalation was typically reported as secondary and not pre-defined finding. Patients requiring intensification were typically on maintenance regimen of 90mg given 8-weekly and had secondary non-response. The response rates to dose escalation were not coherent between studies and long-term outcomes were not recorded. A common conclusion was that although some benefit was noted, further assessment in larger cohorts as well as use of therapeutic drug monitoring is essential to evaluate the usefulness of dose escalation and safety profile of this intervention. Some smaller trials relied on potentially subjective clinical opinion, and so standardised analysis was not possible not only between and also within individual studies. A small number of more recent studies investigated the dose escalation directly and defined dose escalation as primary objective and used recognised methods of quantifying disease activity, e.g. Harvey-Bradshaw Index scores, C-reactive protein or faecal calprotectin levels. Although different treatment intensification strategies were described, detailed analysis is not often available for the subgroups. The authors of these studies report clinical benefits of dose escalation without compromised safety, however, the evidence remains of low grade and the cost-effectiveness has not been evaluated. A manufacturer-sponsored phase IIIb study aimed to assess whether a treat-to-target strategy with early endoscopy, regular biomarker and clinical symptom monitoring, and dose intensification (to 4-weekly) for persistent inflammatory activity, was more successful in achieving endoscopic improvement at week 48 than a clinically driven maintenance strategy in patients with moderate-to-severe active Crohn's disease receiving ustekinumab. 440 patients were randomised 1:1 To receive either standard care or treat-to-target regimen. At week 48 there were no significant findings in endoscopic response, endoscopic remission, mucosal healing and clinical remission between two groups.[5] A very limited amount of evidence to report on use of ustekinumab escalation in ulcerative colitis has been identified. Several studies included investigation of ustekinumab plasma levels and discussion of potential relation to disease control although therapeutic dose monitoring is currently not dose in practice for this drug.[6]
Cost effectiveness and affordability	The overall spend on ustekinumab in Greater Manchester (GM) has nearly doubled from £6,84m in 2019/20 to £13,44 in 2022/23.[7] It was estimated that in 2020/21 between 46-49% of the spent was within gastroenterology.[7] This is the high cost drug with the highest spend across GM since adalimumab came off patent in 2019.

	Ustekinumab has a list price of £2,147 per 130mg vial and the same price for 90mg pre-filled syringe.[8] There is a discount, but this is commercially sensitive. Ustekinumab is protected under patent until 2024.[9] Increasing the dosing interval would double the cost of a year of maintenance therapy from £14,500 for 8-weekly use to £29,000 for 4-weekly use, at list price. As the treatment is not recommended, there will be no increased drug costs to commissioners.
Monitoring	The numbers of individual funding requests (IFRs) for this drug and indication are currently monitored on ad-hoc basis and at minimum 12 monthly. Currently there is no overall GM-wide monitoring of outcomes of drug IFRs.
Patient perspective	A dose escalation of ustekinumab may be the only non-surgical option remaining in some individual cases and if successful could prevent or delay the need for potentially life-changing surgery and need for total parenteral nutrition in case of total colectomy.

Evidence review available on request

[1] GMMMG, High Cost Drugs Pathways for Inflammatory Bowel Disease in Adults (including biologics), version 3.0, June 2019
[2] NICE, TA456 Ustekinumab for moderately to severely active Crohn's disease after previous treatment, July 2017
[3] NICE, TA633 Ustekinumab for moderately to severely active ulcerative colitis, June 2020
[4] Summary of product characteristics. Ustekinumab (Stelara) 90mg solution for injection in pre filled syringe, accessed via www.medicines.org.uk on 12.10.2021
[5] Danese S, Treat to target versus standard of care for patients with Crohn's disease treated with ustekinumab (STARDUST): an open-label, multicentre, randomised phase 3b trial. The Lancet, Gastroenterology & Hepatology, vol 7, issue 4, p294-306, April 2022
[6] Pracz A, Osowska K. Off-label ustekinumab regimens for inflammatory bowel disease including Crohn's disease and ulcerative colitis. Evidence summary, GMJCT, October 2021
[7] HCD data from NHS GM provider trusts accessed via BI tool, IMPCAT, NHS GMIC, July 2023
[8] British National Formulary on-line , accessed via www.medicinescomplete.com, September 2021
[9] https://www.ipo.gov.uk/p-find-spc-byspc-results.htm?number=SPC/GB09/022