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

Ustekinumab (Stelara®▼) for the treatment of inflammatory bowel disease in children and young people aged 6 to 17 years: for ulcerative colitis following loss of response, non-response or intolerance to anti-TNF therapies and vedolizumab; for Crohn's disease following loss of response, non-response or intolerance to anti-TNF therapies (OW25)

May 2024

ONE WALES INTERIM DECISION

Ustekinumab (Stelara®▼) for the treatment of inflammatory bowel disease in children and young people aged 6 to 17 years: for ulcerative colitis following loss of response, non-response or intolerance to anti-TNF therapies and vedolizumab; for Crohn's disease following loss of response, non-response or intolerance to anti-TNF therapies

Date of original advice: February 2023
Date of review: April 2024

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been noted by the All Wales Medicines Strategy Group (AWMSG) and ratified by Welsh Government

Using the agreed starting and stopping criteria, ustekinumab (Stelara®▼) can be made available within NHS Wales for the treatment of inflammatory bowel disease in children and young people aged 6 to 17 years: for ulcerative colitis following loss of response, non-response or intolerance to anti-TNF therapies and vedolizumab; for Crohn's disease following loss of response, non-response or intolerance to anti-TNF therapies.

The risks and benefits of the off-label use of ustekinumab (Stelara®▼) 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 2 years 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 ustekinumab (Stelara®▼) for the treatment of inflammatory bowel disease in children and young people aged 6 to 17 years: for ulcerative colitis following loss of response, non-response or intolerance to anti-TNF therapies and vedolizumab; for Crohn's disease following loss of response, non-response or intolerance to anti-TNF therapies

Starting criteria

Patients aged 6 to 17 years with ulcerative colitis following loss of response or non-response to anti-TNF inhibitors and vedolizumab or when anti-TNF inhibitors and vedolizumab cannot be tolerated or are contraindicated.

Patients aged 6 to 17 years with Crohn's disease following loss of response or non-response to anti-TNF inhibitors or when anti-TNF inhibitors cannot be tolerated or are contraindicated.

Screening

Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. Caution should be exercised when considering the use of ustekinumab in patients with a chronic infection or a history of recurrent infection. Patients should be evaluated for tuberculosis infection and anti-tuberculosis therapy considered prior to initiation of ustekinumab in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed[1,2].

Dose

Induction

Induction treatment is administered intravenously as a weight-based dose of about 6 mg per kg (maximum 520 mg, see also below) administered over one hour.

Child's weight	Dose to be prescribed
<55kg	260mg
55kg- 85kg	390mg
>85kg	520mg

Maintenance

Maintenance treatment is administered as a subcutaneous injection, given at week 8 after induction. Adult patients receive a 90 mg injection, children should receive a body surface area-adjusted dose (considering a standard adult of 1.73 m^2), see suggested dosing below:

Child's weight	Dose to be prescribed
<40kg	45mg
>40kg	90mg

After this, dosing every 12 weeks is recommended. Clinical benefit can be observed from 8 weeks following intravenous induction[3]. Patients who have not had an adequate response 8 weeks after the first subcutaneous dose (week 16) may have a second subcutaneous dose at this time, to allow for delayed response. Patients who lose response on 12-weekly dosing may benefit from an increase in dosing frequency to every 6-8 weeks, according to clinical judgement.

Subcutaneous maintenance doses may be administered at home by the patient or a carer following suitable training.

Outcome data, including dosing frequency and duration of treatment, should be collected to inform future policy changes.

Monitoring

- Infusion-related reactions including anaphylactic shock
- Systemic and respiratory hypersensitivity reactions
- Routine blood tests including FBC, U&E, LFTs, CRP and ESR at induction and 6-monthly thereafter.
- Extra blood tests including vitamins D and B12, folate and ferritin after 6 months of treatment and 6-monthly thereafter.
- Endoscopy (annual)
- Treatment response indicators at induction and 6-monthly thereafter
    - Faecal calprotectin levels
    - Mucosal or endoscopic healing
    - Patient height and weight
    - Paediatric Crohn's Disease Activity Index or Paediatric Ulcerative Colitis Activity Index scores (or appropriate scoring measurements used in clinical practice)

Stopping criteria

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

Outcome data, including reasons for stopping treatment, should be collected to inform future policy changes.

Continuation of treatment

At 12 months, patients should be assessed to determine whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. Regular reassessment to determine whether continued treatment is justified should be done at least every 12 months.

References

1. 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 April 2024.
2. Janssen-Cilag Ltd. STELARA®. 90 mg solution for injection in pre-filled syringe. Summary of Product Characteristics. Oct 2022. Available at: https://www.medicines.org.uk/emc/product/7638/smpc. Accessed April 2024.
3. 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. Accessed April 2024

First Review of One Wales Decision – April 2024

Ustekinumab (Stelara®▼) for the treatment of inflammatory bowel disease in children and young people: for ulcerative colitis following loss of response, non-response or intolerance to anti-TNF therapies and vedolizumab; for Crohn's disease following loss of response, non-response or intolerance to anti-TNF therapies (OW25)

This report was prepared by the All Wales Therapeutics and Toxicology Centre in March 2024. It summarises any new evidence available and patient outcome data collected since the One Wales decision in March 2023.

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. IBD negatively affects the quality of life of children and adolescents based on its impact on the physical, emotional and social wellbeing of these patients, especially if poorly controlled.

Clinicians in Wales consider there is an unmet need and have identified a cohort of people who could benefit from this treatment. This includes children and young people (CYP) aged 6 to 17 years who have failed current treatments in the pathway and where there is no alternative licensed therapy to meet their needs. These patients may be dependent on steroids to control the disease and would be at risk of complications and repeated surgical interventions if their inflammatory bowel disease is poorly controlled. This medicine was therefore considered suitable for assessment via the One Wales process.

Current One Wales Decision: Supported

Licence status: Off-label use for this licensed medicine. [Confidential information removed]

Guidelines: There have been no relevant updates to existing guidelines identified.

Licensed alternative medicines or Health Technology Assessment advice for alternative medicines: No new medicines or Health Technology Assessment advice reported.

Effectiveness: A repeat literature search conducted by AWTTC identified two papers which analysed the clinical effectiveness of ustekinumab pertinent to the recommendation. These included a retrospective study and a systematic review, both published in 2023. Overall results are comparable to those seen in the original evidence report with an indication that benefits with ustekinumab are sustained.

The retrospective study by **Koudsi et al (2023)** evaluated the short- and long-term effectiveness of ustekinumab therapy in paediatric IBD (n = 53). Forty-eight patients (90%) had a diagnosis of CD and 5 (9.4%) had UC. All patients included in this study were resistant to anti-TNF agents prior to receiving ustekinumab. The mean age at diagnosis was 9.8 years old (range 2.3–16 years) and mean disease duration was

6.7 years (range 1.1–13.6 years). The mean and the median duration of follow up were respectively 13 months and 10.5 months (range 1–51 months). The study reported significant improvement in health index and biological parameters. Mean weight increased 3 months after treatment induction, from 45 kg (range 21.5–70.5 kg) at baseline to 49 kg (range 23.3–73 kg) ($p < 0.001$), a significant increase was also reported in body mass index. Paediatric Crohn's Disease Activity Index (PCDAI) and Paediatric Ulcerative Colitis Activity Index (PUCAI) improved with ustekinumab treatment. The mean PCDAI at baseline was 28.7 (range 5-85) decreasing to 18.7 (range 0–75) after 3 months of treatment and dropping to 10 (range 0–35) at the last follow-up. Similarly, the PUCAI showed a significant improvement, 25 (range 15-40) at 3 months and 18.3 (range 0–35) at the last follow-up, compared to 47 (range 25–65) at baseline. At 3 months, levels of the inflammatory marker, C-reactive protein (CRP) was normalised in 75% of patients which is consistent with the equivalent retrospective adult study as well as in the UniStar study included in the previous report. Nine patients (16%) were steroid-free at inclusion, 31 (58%) at 3 months, and 33 (62%) at the last follow-up.

In all patients, the initial intravenous (IV) ustekinumab dose was weight-adjusted (6 mg/kg) and the first subcutaneous (SC) dose was 90 mg, 8 weeks after the first dose. Twenty-four patients were escalated to 4-weekly dosing at 3 months.

During the 13 months of follow-up, 9 patients had adverse effects. The more frequent ones were fatigue in 3 patients (3%) and headache in 3 patients (3%). Ustekinumab treatment was discontinued in 15 patients (28%); this was due to a lack of efficiency in 8 patients (53%), loss of response in 5 patients (33%), recurrent respiratory tract infections in 1 patient (6.7%) and exacerbation of an associated chronic recurrent multifocal osteomyelitis in 1 patient (6.7%).

Fang et al (2023) conducted a systematic review evaluating the efficacy and safety of ustekinumab in paediatric IBD. Eleven studies were included, comprising 370 patients (n = 326 CD patients; n = 44 UC/IBD unspecified patients). Some of these studies were included in the original evidence report.

For CD, the pooled primary outcome of clinical remission rate reported in 6 studies was achieved by 34% (73/204) of patients (range 18.2 to 42.0%) at 8-16 weeks. For maintenance therapy, reported in 4 studies, the pooled remission rate was 46% (60/129) (range 30.3 to 66.67%) at 1 year. In UC patients, only one study reported the clinical remission rate which was 60% at 1 year. The corticosteroid (CS)-free clinical remission rates were 22.73% for CD (one study) and 24% (one study) for UC/IBD-U at 8–16 weeks. For maintenance treatment, the pooled CS-free clinical remission rate in CD patients reported in three studies at 1 year was 45% (42/96) (range 27.3% to 59.5%). These results are consistent with a real-world adult study (ENEIDA). In UC patients, the pooled CS-free clinical remission rate from two studies at 1 year was 46% (16/35) (range 44% to 50%). The differences in clinical response and remission rate should be interpreted with caution due to small patient numbers and variance in definition of response. From five studies, endoscopic remission and response ranged from 0–37.5% (0/5-3/8) and 9.1-100% (1/11 – 8/8) respectively in patients with CD. For UC, only one paediatric study with a small sample size reported an endoscopic improvement rate which was 63.6% (7/11) with median follow-up time of nearly 1 year. About one half (44.2%) of patients required reduction in dose

interval and 62.75% of patients continued ustekinumab therapy at 1 year or until their final visit (week 8-16 or 26, depending on study). Ustekinumab was discontinued in 1.4% (5/370) of patients due to adverse events. Serious adverse events were reported in 3.5% (13/370) of patients. One patient had a suspected anaphylactic reaction to an intravenous re-induction dose but tolerated subsequent subcutaneous doses in a monitored clinical setting.

Safety: Adverse events reported in the studies were consistent with those previously reported, most commonly respiratory tract infection, fatigue and headache. No new safety concerns with ustekinumab were identified. Outcome data provided by the tertiary centre in Cardiff reported no patients discontinuing treatment due to adverse events.

Cost-effectiveness: No relevant cost-effectiveness analyses were identified in the repeat literature search.

Budget impact: Thirteen patients have received treatment with ustekinumab over the last 12 months; twelve at the tertiary centre in Cardiff and Vale UHB and [confidential data removed]. Of these, nine commenced treatment prior to the availability of ustekinumab through the One Wales decision in March 2023; treatment before this would have been initiated following agreement through the Individual Patient Funding Request (IPFR) process. The actual number of patients who received treatment over the past 12 months is lower than the original estimate of 22 new patients per year.

The patent on Stelara® expires in Q1 2024, it is anticipated a number of suppliers will launch biosimilars in Q2 2024, this may reduce the treatment cost originally calculated in the last report.

Impact on health and social care services: Minimal

Patient outcome data: Data have been provided for all thirteen patients. Eleven have been treated for CD, six patients currently remain on an 8-weekly dosing schedule and the remainder are receiving treatment every 4-6 weeks. [Confidential data removed]. The discontinuation rate is comparable to that used in the original submission although higher than that reported in a retrospective study in paediatric CD patients which estimates the probability of remaining on ustekinumab for 12 months to be 76.9%.

Evaluation of evidence

No significant new evidence has been published which challenges the current One Wales advice. The number of children on treatment is lower than the budget impact estimates used in the evidence summary report. Treatment is being tolerated. AWTTC recommends continuing access in Wales to ustekinumab for the treatment of inflammatory bowel disease in children and young people: for ulcerative colitis following loss of response, non-response or intolerance to anti-TNF therapies and vedolizumab; for Crohn's disease following loss of response, non-response or intolerance to anti-TNF therapies.

Next review date: April 2026

References: a full reference list is available on request.

This document includes evidence published since the last review or full assessment of this medicine for the indication under consideration. It does not replace the original full evidence status report. Any previous reviews and the original full evidence status report are available on request by email to AWTTC@wales.nhs.uk.

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.

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