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)

February 2023

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 advice: February 2023

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

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 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 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 December 2022.
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 December 2022.
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 January 2023.

One Wales Medicines Assessment Group summary of decision rationale

Medicine: **ustekinumab (Stelara®▼)**
Indication: **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**
Meeting date: **19 December 2022**

Criteria	OWMAG opinion
Indication	After discussion, OWMAG agreed that the age range of CYP with IBD eligible to receive treatment with ustekinumab should be defined in the indication to those aged from 6 to 17 years. This is to align with the licensed indication for the use of anti-TNF inhibitors for UC and CD in the paediatric population. IPFR remains a route of access for children under 6 years.
Clinical effectiveness	OWMAG notes that the main clinical effectiveness evidence is from a phase III open-label prospective study, a phase I randomised study, two retrospective studies and an observational study. Studies conclude ustekinumab demonstrates efficacy in children and young people (CYP) with otherwise treatment-refractory inflammatory bowel disease. However, results are subject to uncertainty given that there is a lack of placebo-controlled studies in CYP at this time although several phase III clinical trials in the paediatric population are currently underway. The positive reports from experts who had used ustekinumab to treat CYP with IBD were noted most particularly, the resultant reduction in rates of surgery. Many CYP have more aggressive forms of the disease and need earlier intervention with biologics. OWMAG considers that the evidence provided demonstrates clinical effectiveness.
Cost-effectiveness	There is no direct cost-effectiveness evidence available in CYP. However, OWMAG noted that ustekinumab was considered to be cost-effective by NICE for the treatment of adults with ulcerative colitis and Crohn's disease although the relevance of these cost-effectiveness studies to the paediatric population is uncertain. OWMAG acknowledge that disease presentation is usually severe in CYP and there is a large associated cost to the NHS of managing both UC and CD in children and adolescents, most especially as surgery is often required after current licensed treatments have failed to control the disease. Additionally, CYP often need psychological

	support following surgery. It was also noted that the treatment of flares is associated with a significant cost burden to the NHS. OWMAG considers it likely that, taking these factors into account, ustekinumab would also be a cost-effective treatment for CYP as for adults.
Budget impact	OWMAG considers the clinical estimate of patient numbers reported to be reasonable. The group acknowledges that budget impact estimates are subject to uncertainty due to possible variation in dosing intervals and the lack of longer-term discontinuation rate data making it difficult to estimate the proportion of CYP discontinuing treatment throughout the 3-year timeframe. The Clinical experts indicated that the number of CYP being diagnosed is increasing based on better diagnostic monitoring. It was noted by one of the clinical experts that patients will transition in to adult services which would affect patient numbers. This treatment is approved by NICE in adults. OWMAG acknowledges the budget impact is likely to be lower for year one than estimated given that over half of patients are already receiving treatment through IPFR. 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 paediatric patients with IBD which is poorly controlled are at risk of complications and repeated surgical interventions. OWMAG acknowledges the significant burden IBD has on patients' health and health-related quality of life, and how the symptoms of CD and UC, and their unpredictable nature, can be detrimental to both the physical and mental health of CYPs and negatively impact on educational attainment, future work and career choices, and social and emotional interactions and relationships. OWMAG acknowledges that there is an unmet medical need for CYPs who have failed conventional treatments in the pathway, there is no alternative licensed therapy and patients may be dependent on steroids or have to undergo surgery at a formative time in their lives to control the disease. Ustekinumab may offer an effective treatment option for these patients with the potential to prevent or delay surgery.

	It was acknowledged that due to the severity of the disease, some patients may require accelerated dosing regimens.
Final recommendation	OWMAG recommends the use of 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. This recommendation is subject to the development of appropriate start/stop criteria.
Summary of rationale	There is some limited clinical evidence to support ustekinumab as a safe and effective treatment option 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. OWMAG are of the opinion that, as there is no evidence to the contrary, it is reasonable to assume that the efficacy and safety of ustekinumab in CYP from 6 years of age would be similar to that seen in adults. Paediatric patients with IBD which is poorly controlled are at risk of complications and repeated surgical interventions. IBD places a significant burden on both a CYP's physical and mental health and their overall quality of life at this formative time. There are no licensed alternative treatment options and access to ustekinumab for this indication may offer an effective treatment option for these patients and potentially avoid reliance on corticosteroids and/or prevent or delay surgery to control the disease. A proportion of the patient population in Wales are already receiving this treatment via Individual Patient Funding Request, supporting the use on an All Wales basis would ensure equity of access and prevent uneccessary delay.

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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