East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Prescribing Clinical Network

Medicine and proposed indication	Dose escalation - ustekinumab for moderately to severely active Crohn's disease
Reason for PCN consideration	**Proposal to enable dose escalation of ustekinumab (increasing dose frequency to every 8 weeks) for moderately to severely active Crohn's disease, where a patient is losing response (secondary failure).**
Requested by	Gastroenterology specialists and teams

SUMMARY

Clinical Effectiveness

Key points and points for consideration

Gastroenterology Network

- Clinicians express a preference for dose optimisation i.e. dose escalation, with the same agent before moving onto the next available biologic.

NICE

- Clinicians highlighted a response from NICE provided to another enquirer, which said *"that the committee considered a model that allowed for the two alternative dosing regimens for ustekinumab in line with the SPC (one 90mg dose every 12 weeks or one 90mg dose every 8 weeks). It was assumed in the model that remitters would be initiated on 12 week interval dosing and responders who did not achieve remission would be initiated on 8 week interval dosing. The model assumed there was a 2% probability that dosing interval would be changed from 90mg every 12 weeks to 90mg every 8 weeks (based on IM-UNITI trial data). Therefore, in terms of funding, both 12 and 8 weekly dosing should be funded because the model considered by the committee allowed for both dosing regimens".*

Product licence

Crohn's Disease

In the treatment regimen, the first dose of STELARA is administered intravenously. For the posology of the intravenous dosing regimen, see section 4.2 of the STELARA 130 mg Concentrate for solution for infusion SmPC.

The first subcutaneous administration of 90 mg STELARA should take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended.

Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time (see section 5.1).

Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks (see section 5.1).

Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment (see section 5.1).

Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit by week 16 or 16 weeks after switching to the 8-weekly dose.

Immunomodulators and/or corticosteroids may be continued during treatment with STELARA. In patients who have responded to treatment with STELARA, corticosteroids may be reduced or discontinued in accordance with standard of care.

If therapy is interrupted, resumption of treatment with subcutaneous dosing every 8 weeks is safe and effective.

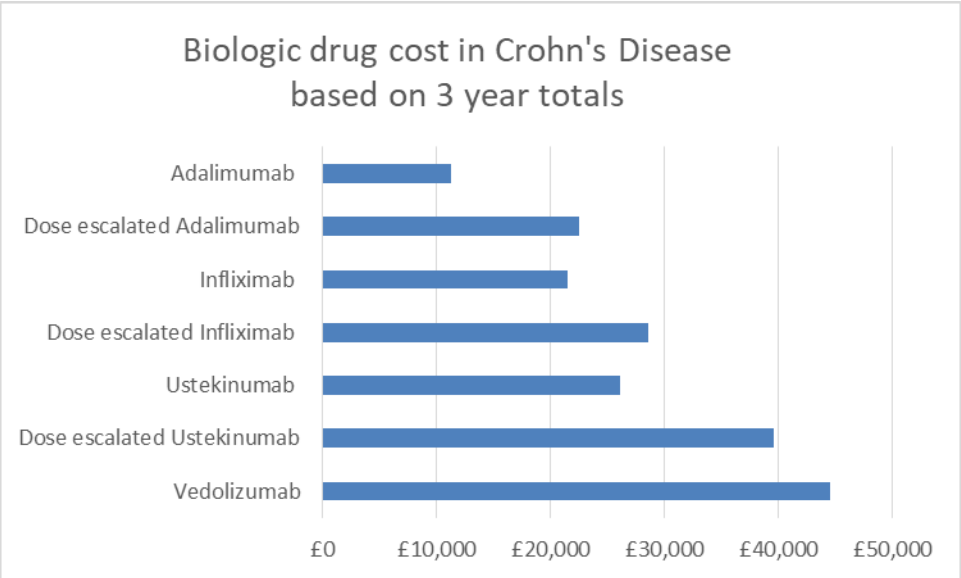
Safety

Summary of the safety profile
The most common adverse reactions (> 5%) in controlled periods of the adult psoriasis, psoriatic arthritis and Crohn's disease clinical studies with ustekinumab were nasopharyngitis and headache. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction that has been reported for STELARA is serious hypersensitivity reactions including anaphylaxis (see section 4.4). The overall safety profile was similar for patients with psoriasis, psoriatic arthritis and Crohn's disease. No new safety concerns were identified with up to 2 years of treatment in patients with Crohn's Disease.

Patient factors

Advantages include the potential recapture of response with ustekinumab prior to switching to an alternative which may improve patient outcomes and could avoid/delay surgery.
Ustekinumab (like the preferred choice of adalimumab) is available as a prefilled syringe for subcutaneous injection. Alternatives of infliximab and vedolizumab require intravenous infusion.

Cost implications



Costs for dose escalation based on maintenance of escalated dose, a proportion of patients will return to standard dose when response recaptured.

Likely place in therapy relative to current treatments

Hospital only initiation and continuation of response to treatment by specialists in Gastroenterology using the blueteq tick box proformas.

It is recommended that these biologic treatments will be initiated where a patient has been fully optimised on conventional therapy such as thiopurines prior to initiation in line with national and local guidance.
These drugs will be considered **RED** on the traffic light system. Read in conjunction with the Biologic Treatment Pathway.

- ustekinumab can be provided by homecare
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Recommendation to PCN

- Recommend that ustekinumab is dose optimised to 8 weekly when a patient starts to lose response to 12 weekly treatment, for short periods (16 weeks) to recapture response.
- Recommend ongoing dose of 8 weekly is commissioned to maintain response if effect lost on return to dose every 12 weeks.
- Recommend that when a patient is in stable clinical remission after 12 months they are encouraged to have a trial withdrawal: NB: A Patient who relapses after trial withdrawal will be able to immediately restart treatment

Potential patient group (if appropriate to include)	
Brief description of disease	Crohn's Disease is a condition that causes inflammation of the digestive system or gut. Crohn's can affect any part of the gut, though the most common area affected is the end of the ileum (the last part of the small intestine), or the colon. The areas of inflammation are often patchy with sections of normal gut in between. A patch of inflammation may be small, only a few centimetres, or extend quite a distance along part of the gut. As well as affecting the lining of the bowel, Crohn's may also go deeper into the bowel wall. It's one of the two main forms of Inflammatory Bowel Disease (IBD). The other is Ulcerative Colitis. Crohn's is a chronic condition. This means that it is ongoing and life-long, patients may have periods of good health (remission), as well as times when symptoms are more active (relapses or flare-ups).
Outcomes required	The aim of treatment is to reduce inflammation in the gut to bring relief from symptoms and induce remission. Once the condition is under control, the aim is to maintain remission and prevent relapse for as long as possible

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	**South East London APC** -Primary and secondary care inflammatory bowel disease pathway. Dose escalation or switching is supported twice only. See attached guidelines here:  SEL IBD pathway final (2).pdf **South West London Commissioning Group** Dose escalation allowed temporarily Ustekinumab 90 mg 8 weekly for 16 weeks with extension to 1 year  2017 18 SWL Biologic Pathway- C
Recommendations from national / regional decision making groups	**Email communication with NICE** On 8th November 2018 following discussion with consultant gastroenterologist colleagues I emailed NICE about ustekinumab for moderately to severely active Crohn's disease after previous treatment. Specifically, if the TA (TA456) evaluated the clinical and cost-effectiveness of 8 weekly dosing. I highlighted a previous response (shared by Janssen-Cilag Ltd) which NICE provided to another enquirer, which read: *"I can confirm that the committee considered a model that allowed for the two alternative dosing regimens for ustekinumab in line with the SPC (one 90mg dose every 12 weeks or one 90mg dose every 8 weeks). It was assumed in the model that remitters would be initiated on 12 week interval dosing and responders who did not achieve remission would be initiated on 8 week interval dosing. The model assumed there was a 2% probability that dosing interval would be changed from 90mg every 12 weeks to 90mg every 8 weeks (based on IM-UNITI trial data). Therefore, in terms of funding, both 12 and 8 weekly dosing should be funded because the model considered by the committee allowed for both dosing regimens".*

	I asked: • Where was it published that the committee considered responders who did not achieve remission would be initiated on 8 week interval dosing with a model of 2% probability? We did not get a costing template for this. • Please could I request that in future technology appraisal documents this information on doses and potential dose increase is made clear? • For TA456 Please could a national statement be released to the effect of your email to Dr Moore to clarify the funding position and avoid postcode difference in interpretation caused by the lack of inclusion of dose extension in the original TA? NICE responded (12th March 2019): I am very sorry for the length of time taken to provide you with a response. As you know, I have needed to liaise with colleagues in the Centre for Health Technology Evaluation at NICE, who oversee the development of NICE technology appraisal (TA) guidance, about the issues you have raised. I can confirm that the model referred to in the response above is the economic model, which was considered by the committee when developing TA456. This model is not published on the website due to confidential data it contains. A costing template was not issued for this appraisal. We only published a resource impact statement. When we develop our technology appraisal guidance, we appraise a treatment within its marketing authorisation (as set out in the SPC). We state this in recommendation 1.1 of the guidance. Unless we specify a specific dose or duration of treatment (or other criteria) within our recommendations, then the treatment should be available within the terms of the marketing authorisation, as set out in the SPC (when considered appropriate by the clinician). With regards to adding a clarifying statement to the website, we do not consider that such a statement should be added to the page for TA456. However, we do consider it appropriate to amend section 2 of the guidance, which contains a brief summary of the SPC, (specifically, the 'Recommended dose and schedule' information) to more fully reflect the SPC in terms of the option of increasing dose frequency to every 8 weeks, to make it clearer that this is not excluded. This amendment will be made as soon as possible to our website. In addition, we are in the early stages of reviewing the Achieving and demonstrating compliance with NICE TA and HST guidance page of our website, and as part of this will consider whether it would be appropriate to add additional wording here, regarding implementing TA guidance within the terms of the marketing authorisation (unless otherwise stated by the guidance). Once again, please accept my apologies for the unexpected delay in responding to your concerns. Corporate Communications National Institute for Health and Care Excellence

Stakeholder views	See comments from specialists at the foot of this review
CCG priorities	The Sustainability and Transformation Plans (STPs) and the CCGs priorities are to provide equitable therapy across the health economy, promoting optimisation of pre-biologic use such as thiopurine as per the British Society of Gastroenterology Guidelines and NICE guidance.

References

References

1. NICE Ustekinumab for moderately to severely active Crohn's disease after previous treatment https://www.nice.org.uk/guidance/ta456
2. STELARA 45mg solution for injection in pre filled syringe SPC -updated on eMC 16 Jan 2019 https://www.medicines.org.uk/emc/product/7639/smpc#
3. Guidelines for the management of inflammatory bowel disease in adults Gut 2011;60:571e607. doi:10.1136/gut.2010.224154

Date: 18th March 2019

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VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
V1	18/03/19	Liz Clark	DRAFT	
V2				
V3				