

ustekinumab 130mg concentrate for solution for infusion and 90mg solution for injection (Stelara®) SMC No. (1250/17)

Janssen-Cilag Ltd

09 June 2017

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

ustekinumab (Stelara®) is accepted for use within NHS Scotland.

Indication under review: for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNF α) antagonist or have medical contraindications to such therapies.

Ustekinumab was associated with improved clinical response and remission versus placebo during induction and maintenance treatment in patients with moderately to severely active Crohn's disease who had failed to respond to or not tolerated conventional therapy or TNF α antagonists.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of ustekinumab. The advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

**Chairman,
Scottish Medicines Consortium**

Indication

For the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF α [tumour necrosis factor-alpha] antagonist or have medical contraindications to such therapies.^{1,2}

Dosing Information

Ustekinumab treatment is to be initiated with a single intravenous (IV) dose (using the 130mg concentrate for solution for infusion formulation) based on body weight of the patient at the time of dosing (approximately 6 mg/kg): ≤ 55 kg a 260mg IV dose (two vials); >55 kg to ≤ 85 kg a 390mg dose (three vials) and >85 kg a 520mg dose (four vials). Ustekinumab 130 mg concentrate for solution for infusion is for IV use only and should be administered over at least one hour.

The first subcutaneous (SC) dose of 90mg should be given at week 8 following the IV dose using the 90mg solution for injection formulation. After this, dosing every 12 weeks is recommended.

Patients who have not shown adequate response at 8 weeks after the first SC dose, may receive a second SC dose at this time. Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks. Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment. 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 ustekinumab. In patients who have responded to ustekinumab treatment, corticosteroids may be reduced or discontinued in accordance with standard of care.

If therapy is interrupted, resumption of treatment with SC dosing every 8 weeks is safe and effective.^{1,2}

Product availability date

November 2016

Summary of evidence on comparative efficacy

Ustekinumab is a fully human IgG1k monoclonal antibody which binds specifically to the shared p40 protein subunit of human cytokines IL-12 and IL-23 which are secreted by activated antigen presenting cells. It is thought that ustekinumab interrupts cytokine pathways integral to the pathology of Crohn's disease.^{1,2} An intravenous (IV) formulation of ustekinumab has been developed specifically for induction treatment of Crohn's disease in addition to the existing subcutaneous (SC) formulation which is licensed for plaque psoriasis and psoriatic arthritis and now also for maintenance treatment of Crohn's disease.¹⁻³

Evidence to support the use of ustekinumab in Crohn's disease comes from three, randomised, double-blind, phase III studies: two for induction treatment (UNITI-1 and UNITI-2) and one for maintenance treatment (IM-UNITI). UNITI-1 and UNITI-2 had the same methodology but differed in terms of previous treatments. Eligible patients were aged ≥ 18 years, with a history of Crohn's disease for ≥ 3 months and a Crohn's Disease Activity Index (CDAI: range 0 to 600) score of 220 to 450 indicating moderate to severe disease. They had evidence of active disease with C-reactive protein (CRP) $>3.0\text{mg/L}$, faecal calprotectin $>250\text{mg/kg}$ bodyweight or endoscopic ulceration in the ileum, colon or both. For UNITI-1, patients were required to have received at least one TNF α antagonist (infliximab, adalimumab or certolizumab pegol) and not responded initially (primary non-responder), responded initially but then lost response (secondary non-responder) or were unable to tolerate the medicine. For UNITI-2, patients were required to have failed treatment or had unacceptable side effects with immunosuppressants (i.e. azathioprine, 6-mercaptopurine or methotrexate) or corticosteroids. Although previous treatment with at least one TNF α antagonist was allowed in UNITI-2, patients must not have had unacceptable side effects nor primary or secondary non-responses.⁴

In both studies, patients were randomised equally to receive ustekinumab 130mg IV infusion, ustekinumab 6mg/kg IV infusion (i.e. licensed regimen) or placebo at week 0. Randomisation was stratified by region and CDAI score (≤ 300 or >300) and also by initial response to TNF α antagonists (yes or no) in UNITI-1. Patients were allowed to continue the following medicines provided that doses were stable for at least three weeks before baseline: oral 5-aminosalicylates, oral corticosteroids (prednisone-equivalent dose of ≤ 40 mg/day or ≤ 9 mg/day of budesonide) or antibiotics for Crohn's disease. In addition, patients who were receiving conventional immunosuppressants (i.e. azathioprine, 6-mercaptopurine or methotrexate) must have been taking them for at least 12 weeks and on a stable dose for at least the previous four weeks.^{3, 4}

The primary outcome in both studies was clinical response at week 6 (CDAI-100, defined as a decrease in CDAI score of ≥ 100 ; or in those with a baseline CDAI score of ≥ 220 to ≤ 248 , CDAI score <150).^{3, 4} This was achieved by significantly more ustekinumab than placebo patients. Key secondary outcomes included clinical remission at week 8 (defined as CDAI score <150), clinical response at week 8, 70-point clinical response (CDAI-70: defined as reduction in CDAI score of ≥ 70) at weeks 3 and 6. Results for the licensed dose of ustekinumab (6mg/kg) and placebo are presented in table 1. There were greater reductions in CRP and faecal calprotectin in the ustekinumab than placebo group in both studies.⁴

Table 1: primary and key secondary outcomes in induction studies (UNITI-1 and UNITI-2)

	UNITI-1		UNITI-2	
	Ustekinumab 6mg/kg (n=249)	Placebo (n=247)	Ustekinumab 6mg/kg (n=209)	Placebo (n=209)
Clinical response at week 6, n (%)	84 (34%)	53 (21%)	116 (56%)	60 (29%)
Difference versus placebo, % (95% CI), p-value	12% (4.5 to 20), p<0.01		27% (18 to 36), p<0.001	
Clinical remission at week 8, n (%)	52 (21%)	18 (7.3%)	84 (40%)	41 (20%)
Difference versus placebo, % (95% CI), p-value	14% (7.6 to 20), p<0.001		21% (12 to 29), p<0.001	

Clinical response at week 8, n (%)	94 (38%)	50 (20%)	121 (58%)	67 (32%)
Difference versus placebo, % (95% CI), p-value	18% (9.7 to 25), p<0.001.		26% (17 to 35), p<0.001	
70-point clinical response at week 3, n (%)	101 (41%)	67 (27%)	106 (51%)	66 (32%)
Difference versus placebo, % (95% CI), p-value	13% (5.2 to 22), p<0.001		19% (9.9 to 28), p<0.001	
70-point clinical response at week 6, n (%)	109 (44%)	75 (30%)	135 (65%)	81 (39%)
Difference versus placebo, % (95% CI), p-value	13% (5.0 to 22), p<0.01		26% (17 to 35), p<0.001	

CI=confidence interval

Quality of life was assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ) and the Short Form (36) Health Survey (SF36). In UNITI-1 and UNITI-2, patients in the ustekinumab groups had statistically significantly greater and clinically meaningful improvements in IBDQ total score and SF-36 Mental Component Summary Score at week 8 and also in SF-36 Physical Component Summary Score in UNITI-2 at week 8 compared with patients in the placebo groups.

3

Patients who completed UNITI-1 and UNITI-2 and who achieved a clinical response (as defined previously) to ustekinumab induction treatment, assessed at week 8, were eligible for randomisation into the primary population (n=388) of the maintenance study (IM-UNITI). They were randomised equally to receive ustekinumab 90mg SC every 8 weeks, ustekinumab 90mg SC every 12 weeks or placebo SC. Randomisation was stratified by the ustekinumab dose used during the induction studies and by remission status at week 0. Patients receiving corticosteroids at week 0 were to taper the dose. The primary outcome, clinical remission (defined as CDAI <150) at week 44, was achieved by significantly more ustekinumab than placebo patients: 49% (63/129) of patients in the ustekinumab 90mg SC every 12 weeks, 53% (68/128) of patients in ustekinumab 90mg SC every 8 weeks group and 36% (47/131) of patients in the placebo group. The differences versus placebo were 13% (95% CI: 1.1 to 25), p=0.04 for the 12-weekly group and 17% (95% CI: 5.3 to 29), p= 0.005 for the 8-weekly group.^{3, 4}

The major secondary outcomes included clinical response (CDAI-100) at week 44, which was achieved by significantly more ustekinumab than placebo patients: 58%, 59% and 44% respectively. Clinical remission at week 44 in the subgroup of patients in clinical remission at week 0 (i.e. maintenance of remission) was achieved by numerically more ustekinumab 90mg SC every 12 weeks and significantly more ustekinumab 90mg SC every 8 weeks patients than placebo (56% and 67% versus 46% respectively). Corticosteroid-free remission at week 44 was achieved by more ustekinumab than placebo patients: 43% and 47% versus 30% respectively.^{3, 4} The improvements in IBDQ and SF36 achieved during induction were generally more likely to be maintained to week 44 in ustekinumab than placebo patients in the IM-UNITI study.³

An endoscopy substudy was performed in 252 patients from UNITI-1 and-2 who underwent colonoscopies at weeks 0 and 8. The primary outcome, the change in the simplified endoscopic

activity score for Crohn's disease (SES-CD) from baseline to week 8, was significantly greater for both ustekinumab doses pooled (n=155) than placebo (n=97) (-2.8 versus -0.7, respectively, p=0.012).^{1, 2, 5}

Summary of evidence on comparative safety

The safety profile of ustekinumab in Crohn's disease was consistent with that already known for psoriasis and psoriatic arthritis.³

During the 8-week induction studies, an adverse event was reported in 66% (164/249) of ustekinumab patients and 65% (159/245) of placebo patients in UNITI-1 and 56% (115/207) of ustekinumab patients and 54% (113/208) of placebo patients in UNITI-2. These were considered serious in 7.2% and 6.1% of patients respectively in UNITI-1 and 2.9% and 5.8% of patients respectively in UNITI-2. In the ustekinumab groups, the most frequently reported adverse events were arthralgia, headache, nausea, pyrexia, nasopharyngitis, abdominal pain, Crohn's disease event and fatigue. In UNITI-1, infections were reported in 26% of ustekinumab and 24% of placebo patients and were considered serious in 2.8% and 1.2% respectively. An infusion-related adverse event was reported in 3.6% and 2.0% of patients respectively. In UNITI-2, infections were reported in 22% of ustekinumab and 23% of placebo patients and were considered serious in 0.5% and 1.4% respectively. An infusion-related adverse event was reported in 1.4% and 2.9% of patients respectively.⁴

During the 44-week IM-UNITI study, an adverse event was reported in 80% (106/132) of ustekinumab 90mg every 12 weeks patients, 82% (107/131) of ustekinumab 90mg every 8 weeks patients and 84% (111/133) of placebo patients and these were considered serious in 12% (16/132), 9.9% (13/131) and 15% (20/133) respectively.⁴ The most commonly reported were similar to the induction studies. Infections were reported in 46%, 48% and 50% of ustekinumab 90mg every 12 week, ustekinumab 90mg every 8 weeks and placebo patients respectively and were considered serious in 5.3%, 2.3% and 2.3% respectively. An injection-site adverse event was reported in 2.3%, 6.9% and 0.8% of patients respectively.⁴

There were no deaths or cases of reversible posterior leukoencephalopathy syndrome during the studies.⁴

Summary of clinical effectiveness issues

Crohn's disease is a chronic, relapsing remitting, inflammatory condition involving various parts of the gastrointestinal tract. Patients suffer recurrent attacks of acute symptoms followed by periods of remission with no or reduced symptoms. Treatment of Crohn's disease is aimed at relieving symptoms: in acute disease to induce remission and then to maintain remission and prevent relapse. Conventional therapy includes corticosteroids, aminosalicylates and immunosuppressants. The TNF α antagonists (infliximab and adalimumab) are licensed for patients with moderately to severely active Crohn's disease who have not responded to, been intolerant to, or had a contraindication to a corticosteroid and/or an immunosuppressant. In line with the NICE multiple technology appraisal, infliximab and adalimumab are accepted for the treatment of severe active Crohn's disease in NHS Scotland given as a planned course of treatment until treatment failure or until 12 months after the start of treatment, whichever is shorter. Vedolizumab is a monoclonal antibody, licensed, like ustekinumab, for patients with moderately

to severely active Crohn's disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a TNF α antagonist. SMC has recommended it for restricted use for those patients who have had an inadequate response with, lost response to, or were intolerant to a TNF α antagonist. The clinical experts consulted by SMC have indicated that there is a clinical need for additional treatments in this patient population.

In the pivotal induction and maintenance studies, the primary outcomes of clinical response and remission are direct health outcomes and were assessed according to the CDAI score. This is acknowledged by the European Medicines Agency (EMA) as not being an ideal measure and is currently under review. In the induction studies, a significantly greater proportion of patients achieved a clinical response at week 6 with the licensed dose of ustekinumab than with placebo. Improvements in clinical response and remission with ustekinumab were evident from week 3 onwards. In the maintenance study, a significantly greater proportion of patients achieved clinical remission with ustekinumab administered every eight or 12 weeks than placebo. Although the EMA notes that the primary outcome differed from that recommended (maintained steroid-free remission without surgery for at least 12 months), it was acknowledged that ustekinumab was being developed for patients with Crohn's disease who had not achieved a successful outcome with currently available therapies and for whom options were therefore restricted. In this population, a primary outcome of clinical remission was considered clinically important and this was supported by more patients treated with ustekinumab than placebo achieving steroid-free remission at week 44 of IM-UNITI.³ The duration of follow-up in both the induction and maintenance studies was shorter than recommended by EMA guidance. However since the studies were designed before this was published, the EMA considered the outcomes were acceptable. In addition, IM-UNITI is followed by an ongoing extension study.³

During the maintenance study, the treatment effect of ustekinumab was numerically greater with the 8-weekly dosing compared with the 12-weekly dosing but this was counterbalanced by a higher rate of adverse events. The EMA therefore recommended the dose of 90mg SC every 12 weeks as the standard maintenance dose which could be increased to every 8 weeks in the case of inadequate response.³

Study patients reflected those likely to be treated with ustekinumab in clinical practice. Differences between the inclusion criteria of UNITI-1 and UNITI-2 in terms of previously failed treatment resulted in patients in UNITI-1, who had failed TNF α antagonist treatment, having more severe, refractory disease than those in UNITI-2. Approximately half of these patients had a history of failure with two or three TNF α antagonists. Subgroup analyses in all studies indicated that the treatment effect of ustekinumab was consistent across the pre-specified subgroups.^{3, 4}

The summary of product characteristics states that 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. However in IM-UNITI, randomised patients were to have a response at week 8 although those not responding to ustekinumab induction at week 8 were given SC ustekinumab in the non-randomised arm of the study. Of patients not achieving a response at week 8 following induction and who subsequently received a SC dose of ustekinumab, 50% achieved a clinical response at week 16 (post induction).^{1, 2}

There are no comparative data with other medicines for Crohn's disease and the submitting company presented network meta-analyses (NMAs) to compare ustekinumab with infliximab, adalimumab and vedolizumab. Separate NMAs were performed for induction and maintenance treatment further separated according to failure or intolerance to conventional therapy or TNF α antagonists. A total of 11 studies were included in the NMAs and clinical outcomes compared

were clinical response (assessed as CDAI-70 and CDAI-100) and clinical remission (CDAI <150). There were no data to allow infliximab to be included in the TNF α antagonist failure subpopulation networks. The NMAs of induction treatment used Bayesian methods and found no evidence of difference between ustekinumab and adalimumab in the conventional therapy failure subpopulation and between ustekinumab and vedolizumab or adalimumab in the TNF α antagonist failure subpopulation. In the conventional therapy failure subpopulation, infliximab appeared superior to ustekinumab as induction treatment. However, since the only evidence for infliximab was old and based on small patient numbers, this comparison should be interpreted with caution. Due to differences between the maintenance studies in terms of carry-over effect from induction treatment and re-randomisation methods and criteria, a standard NMA using placebo as a common comparator was not considered feasible. Instead, the company performed treatment sequence analyses which suggested no evidence of difference in clinical response or remission between ustekinumab and adalimumab in the conventional therapy failure and between ustekinumab and vedolizumab or adalimumab in the TNF α antagonist failure subpopulation. There are a number of issues affecting the validity of these results including differences between the study populations (especially for adalimumab studies which excluded patients who failed to respond initially to infliximab), limited data for infliximab, clinical outcomes measured at different time-points in the individual studies, variation in results in the placebo groups of individual studies. There was greater heterogeneity between studies for maintenance treatment increasing the uncertainty of the NMA results for the treatment sequence analyses. The relative safety of ustekinumab and comparators was not assessed but in a published NMA rates of adverse events were similar with biologic medicines.⁶

The introduction of ustekinumab would offer an alternative treatment with a different mechanism of action for patients with moderately to severely active Crohn's disease. In patients who have failed on or are unable to tolerate TNF α antagonists, the current treatment options are limited to vedolizumab and surgery. Therefore ustekinumab could fulfil an unmet need in these patients. The administration requirements are simpler for ustekinumab (6mg/kg IV infusion at week 0 followed by 90mg SC at week 8 and then every 12 weeks thereafter) than for vedolizumab (300mg IV at weeks 0, 2 and 6 and then every 8 weeks thereafter) and may offer the potential for patients to self-administer maintenance ustekinumab at home. During the maintenance study, administration of ustekinumab also allowed a reduction in the use of corticosteroids.^{3, 4}

Summary of comparative health economic evidence

The company presented a cost-minimisation analysis which evaluated the cost-effectiveness of ustekinumab in two patient groups. The first subpopulation compared ustekinumab with adalimumab and infliximab (including the biosimilar products) in patients who have failed conventional care. The second subpopulation compared ustekinumab with vedolizumab and adalimumab in patients who have failed TNF treatment.

The time horizon for the base case analysis was one year and costs were calculated for an induction and maintenance period. At the start of the maintenance phase patients could receive either low or high doses of the various medicines and the analysis modelled a proportion of patients who transitioned from low to high doses every two weeks. It is worth noting that ustekinumab 130mg for infusion was delivered in the induction phase while patients received 90mg for injection in the maintenance phase.

Data to support the comparable efficacy of ustekinumab and the comparators were taken from the NMAs described above. The IM-UNITI study was used to estimate the proportion of patients who received low and high dose ustekinumab at the start of the maintenance phase as well as the two weekly probability of moving to high dose ustekinumab. For the comparators, all patients started the maintenance phase receiving the low dose of the respective medicines. The two weekly probability of moving to high dose adalimumab was taken from the CHARM study with values for infliximab (and the biosimilar products) assumed to be the same as adalimumab.⁷ The two weekly probability of moving to high dose vedolizumab was assumed to be the same as ustekinumab. The UNITI-1 and UNITI-2 studies informed the distribution of patient weight used in the analysis for patients who received ustekinumab.

The cost minimisation analysis focused on medicines and administration costs.

The base case results and key sensitivity analyses are summarised in tables 2 and 3 below.

Table 2: Results for conventional care failure population

Analysis	Ustekinumab Total cost at list price	Inc. cost vs adalimumab	Inc. cost vs infliximab (Resima®)	Inc. cost vs infliximab (Inflectra®)	Inc. cost vs infliximab (Remicade®)
Base case	£16,980	£3,494	-£1,614	-£1,614	-£3,207
2 year treatment discontinuation	£29,557	£1,505	-£9,062	-£9,062	-£12,507
3 year treatment discontinuation	£40,374	-£3,253	-£16,310	-£16,310	-£21,464
Same 2-week probability of dose-escalation	£16,980	£4,206	-£978	-£978	-£2,500
Life time horizon: low doses*	£243,792	£9,940	-£59,665	-£59,664	-£87,755
Life time horizon: high doses*	£361,600	-£105,049	-£191,670	-£191,669	-£247,516

*analyses used the standard induction dose for adalimumab

Table 3: Results for TNF failure population

Analysis	Ustekinumab Total Cost at list price	Inc. cost vs adalimumab	Inc. cost vs vedolizumab using list price for vedolizumab
Base case	£17,152	£3,666	-£8,422
2 year treatment discontinuation	£29,902	£1,850	-£18,678
3 year treatment discontinuation	£40,822	-£2,806	-£33,954
Same 2-week probability of dose-escalation	£17,152	£4,378	-£8,422
Life time horizon: low doses*	£243,655	£9,812	-£151,541
Life time horizon: high doses*	£361,472	-£105,176	-£419,716

*analyses used the standard induction dose for adalimumab

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented. With the PAS, ustekinumab became a cost-effective treatment option.

A PAS is in place for the comparator vedolizumab and when an estimate of the PAS was included and used for decision making, ustekinumab became less cost-effective. SMC is unable to present the results provided by the company which used an estimate of the PAS price for vedolizumab due to commercial confidentiality and competition law issues.

The main weaknesses were:

- No direct data were available which supported the equivalent efficacy of the medicines under review and therefore equivalent efficacy was justified on the basis of the NMAs. The NMAs were associated with a number of limitations however following discussions at the SMC the NMAs were considered sufficiently robust to support the cost-minimisation analysis.
- The economic model enabled patients to start maintenance treatment on low or high doses of the various medicines as well as dose escalate throughout the analysis. This added a degree of complexity to the analysis and it may have been simpler to present analyses using the different doses separately. The time horizon used in the analysis was considered relatively short as SMC experts indicated patients may remain on treatment for a number of years. The base case analysis also used a rapid induction dose for adalimumab which was more costly than the standard induction dose. To address these uncertainties the company provided a combined analysis which considered high and low doses separately, used a life time horizon and included the standard induction dose for adalimumab. The results are presented in Table 2 and 3 above.

Despite the above uncertainties the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Crohn's and Colitis UK, which is a registered charity.
- Crohn's and Colitis UK has received 4.6% pharmaceutical company funding in the past two years, including from the submitting company.
- Living with Crohn's disease is extremely difficult. The frequent and urgent need for the toilet, together with loss of sleep and the invisible symptoms of pain and continual or profound fatigue, can severely affect patient's self-esteem and social functioning. For many patients the fear of incontinence can have a devastating impact as it limits their ability to engage in activities such as going to work, shopping and socialising. There can also be significant impacts on family life.
- A significant proportion of patients do not respond to, or cannot tolerate currently available

treatment options. These patients are left with a very poor quality of life. Ustekinumab may provide another treatment option for these patients.

- This new medicine is important to patients and carers because it offers a new treatment option with a different mode of action. Unlike the current treatments, it targets interleukin 12 and interleukin 23, naturally occurring proteins that play a role in immune-mediated inflammatory disorders.
- Ustekinumab offers hope to patients for whom current therapies are ineffective.

Additional information: guidelines and protocols

The European Crohn's and Colitis Organisation (ECCO) produced an evidence based consensus guideline "The third European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: diagnosis and medical management" in September 2016.⁸ For patients with moderately or severely active localised ileocaecal Crohn's disease, a TNF α antagonist is recommended for patients who have previously been steroid-refractory or intolerant. For patients refractory to steroids and/or TNF α antagonists, vedolizumab is an appropriate alternative; patients with severely active Crohn's disease and for patients who are disease refractory to conventional medical treatment, surgery is a reasonable alternative. The guideline states that all currently available TNF α antagonists appear to have similar efficacy in luminal Crohn's disease and similar adverse-event profiles, so the choice depends on availability, route of delivery, patient preference and cost. Where there is loss of response to TNF α antagonist therapy, ECCO recommend that switching to an alternative TNF α antagonist is effective but that dose escalation or a reduction of treatment intervals are also appropriate initial options.

The National Institute for Health and Care Excellence (NICE) published clinical guideline 152 "Crohn's Disease: management" in October 2012 updated in May 2016 with a new recommendation on induced remission.⁹ NICE recommendations on infliximab and adalimumab are from "Infliximab (review) and adalimumab for the treatment of Crohn's disease (NICE [multiple] technology appraisal guidance 187)" which was published in May 2010.¹⁰ NICE recommend that infliximab and adalimumab should be considered in adult patients who have failed to respond or are intolerant to conventional therapy, including immunosuppressant and steroid treatments. Treatment should be continued for 12 months or until treatment failure; patients should then have their disease reassessed to determine if ongoing treatment remains clinically appropriate. Patients should have the option to start treatment again if relapses occur once the medicine has stopped. Patients should be monitored to ensure ongoing treatment remains clinically appropriate. In the 2016 update to this guideline, NICE recommends patients are made aware at the start of treatment on options for monotherapy or combined therapy [infliximab or adalimumab combined with immunosuppressant therapy] and the uncertainty surrounding the comparative effectiveness and long-term adverse effects of these.

The British Society of Gastroenterology (BSG) published an evidence based consensus "Guidelines for the management of inflammatory bowel disease in adults" in 2011.¹¹ The guideline committee endorses the recommendations made by NICE regarding treatment of patients with severely active Crohn's disease with infliximab and adalimumab although notes the lack of evidence to support the optimal selection of patients and the timing of stopping TNF α antagonist therapy.

Additional information: comparators

TNF α antagonists (infliximab or adalimumab) or vedolizumab.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
Ustekinumab	6mg/kg IV then 90mg SC at week 8 then every 12 weeks*	First year: 15,029 Subsequent years: 8,588
Vedolizumab	300mg IV at week 0, 2 and 6, then every 8 weeks	16,400 Subsequent years: 12,300 to 14,350
Adalimumab	80mg SC (or rapid induction with 160mg at week 0 and 80mg at week 2) then 40 mg alternate weeks	First year: 9,860 (10,917) Subsequent years: 9,156
Infliximab**	5 mg/kg IV at weeks 0, 2 and 6 weeks, then every 8 weeks	First year: 12,064 to 13,428 Subsequent years: 9,048 to 10,071

Doses are for general comparison and do not imply therapeutic equivalence. Costs for vedolizumab and adalimumab from eVadis on 3 April 2017 and costs for ustekinumab and infliximab from MIMs April 2017. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs for ustekinumab and infliximab are based on a bodyweight of 70kg. if there is an adequate response ustekinumab dosing can be increased to 90mg SC every 8 weeks which cost £12,882/year. **Costs for infliximab reflect the range of list prices for the reference product and biosimilar products Costs do not take any patient access schemes into consideration. IV=intravenous, SC=subcutaneous*

Additional information: budget impact

The same patient numbers were estimated for the conventional care and TNF α antagonist failure populations. The company estimated 999 patients would be eligible for treatment in year 1 rising to 1,172 patients in year 5. A discontinuation rate of 11% was also included for all years in the analysis.

Conventional Care failure population

The uptake rate was estimated to be 1% in year 1 (9 patients) and 10% in year 5 (104 patients).

TNF α antagonist failure population

The uptake rate was estimated to be 5% in year 1 (44 patients) and 60% in year 5 (626 patients).

Other data were also assessed but remain commercially confidential.*

References

1. Janssen Cilag Ltd. Summary of product characteristics for ustekinumab (Stelara) 45mg and 90mg solution for injection. Last updated 15 November 2016.
2. Janssen Cilag Ltd. Summary of product characteristics for ustekinumab (Stelara) 130mg concentrate for solution for infusion. Last updated 15 November 2016.
3. European Medicines Agency. Public assessment report for ustekinumab (Stelara) EMEA/H/C/000958/X/0049/G, 15 September 2016.
4. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, *et al.* Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. *New England Journal of Medicine.* 2016;375(20):1946-60.
5. Rutgeerts P, Gasink C, Chan D, Lang Y, Pollack PF, Hanauer S, *et al.* Efficacy of Ustekinumab for Induction and Maintenance of Endoscopic Healing in Patients with Crohn's Disease. *United European Gastroenterology (UEG) Week 2016, Basow, DS (Ed), Vienna; 2016.*
6. Mocko P, Kawalec P, Pilc A. Safety profile of biologic drugs in the therapy of Crohn's disease: a systematic review and network meta-analysis. *Pharmacol Rep* 2016;68:1237-43.
7. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology.* 2007;132(1):52-65.
8. Gomollon F, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, *et al.* 3. EUROPEAN Evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: Diagnosis and medical management. *J Crohns Colitis.* 2016. Epub 2016/09/24.
9. National Institute for Health and Care Excellence (NICE) Clinical Guideline 152: Crohn's disease management. Published October 2012, last updated May 2016.
10. National Institute for Health and Care Excellence (NICE). TA187: Infliximab (review) and adalimumab for the treatment of Crohn's disease. 2010 [cited; Available from: <https://www.nice.org.uk/guidance/ta187>].
11. Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, *et al.* Guidelines for the management of inflammatory bowel disease in adults. *Gut.* 2011;60(5):571-607.

This assessment is based on data submitted by the applicant company up to and including 11 May 2017.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*

http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates

separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.