Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2250

ustekinumab 130mg concentrate for solution for infusion and 90mg solution for injection (vials) and solution for injection in pre-filled syringe (Stelara®)

Janssen-Cilag Ltd UK

06 March 2020

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

ustekinumab (Stelara®) is accepted for use within NHSScotland.

Indication under review: For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.

In a phase III study in patients with moderate to severe ulcerative colitis who had failed prior therapy, clinical remission was achieved by a significantly greater proportion of patients who received ustekinumab compared with placebo.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies.[1, 2]

Dosing Information

Ustekinumab treatment is to be initiated with a single intravenous dose based on body weight as detailed in Table 1 below. It should be administered over at least one hour.

Table 1: Ustekinumab initial intravenous dose

Body weight of patient at the time of dosing	Recommended dose[a]	Number of 130mg ustekinumab vials
≤55kg	260mg	2
>55kg to ≤85kg	390mg	3
>85kg	520mg	4

[a]Approximately 6mg/kg

The first subcutaneous administration of 90mg should be given at week 8 following 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.

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 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose.

Ustekinumab is intended for use under the guidance and supervision of physicians experienced in the diagnosis and treatment of ulcerative colitis.

Refer to the Summary of product characteristics (SPC) for further details.[1, 2]

Product availability date

3 September 2019

Summary of evidence on comparative efficacy

Ustekinumab is a fully human IgG1κ monoclonal antibody that inhibits the bioactivity of human cytokines interleukin (IL)-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Abnormal regulation of IL-12 and IL-23 has been

associated with immune mediated diseases, including ulcerative colitis.[1-3] Ustekinumab is the first IL-12/IL-23 inhibitor to be licensed for use in ulcerative colitis.

Key evidence for this indication is from the UNIFI induction and maintenance studies. These were randomised, double-blind, placebo-controlled, phase III studies conducted under a single protocol but designed and analysed as two separate studies with separate outcomes controlled for Type I error. UNIFI recruited adults with moderate-to-severe ulcerative colitis, defined as a total score of 6 to 12 on the Mayo scale and a sub-score of 2 or 3 on the endoscopic component of the Mayo scale. The Mayo score includes four components (stool frequency, rectal bleeding, findings of endoscopy and physician's global assessment) with scores of each ranging from 0 to 3, giving a total score of 0 to 12 (higher score indicating more severe disease). Recruited patients had an inadequate response to, or unacceptable side effects from tumour necrosis factor (TNF) inhibitors, vedolizumab, or conventional therapy.[3, 4]

In the induction study, patients were randomly assigned in a 1:1:1 ratio to receive a single intravenous (IV) infusion of 130mg of ustekinumab, a weight-range–based dose of approximately 6mg/kg (the licensed dose) of ustekinumab, or placebo, stratified by previous treatment failure with biologic agents (yes or no) and geographic region (Eastern Europe, Asia, or Rest of World).[3, 4]

Patients who had a clinical response to IV ustekinumab at week 8 entered the maintenance study. Patients who did not have a clinical response to placebo received an induction dose of IV ustekinumab (6mg/kg) at week 8 and those who had a clinical response at week 16 also entered the maintenance study. Clinical response was defined as a decrease in the total Mayo score of ≥30% and of ≥3 points from baseline, with an accompanying decrease of ≥1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1.[3, 4] These patients were randomly assigned, in a 1:1:1 ratio, to receive subcutaneous (SC) injections of 90mg ustekinumab every 12 weeks, 90mg ustekinumab every 8 weeks, or placebo through week 44, stratified by IV induction treatment (ustekinumab 130mg, ustekinumab 6mg/kg, or placebo followed by ustekinumab 6mg/kg), clinical remission at baseline of the maintenance study (yes or no), and oral corticosteroid use at baseline of the maintenance study (yes or no). This was the primary analysis population.[3, 4]

Patients who did not have a response to IV ustekinumab at week 8 received 90mg SC ustekinumab in a blinded manner and were re-evaluated at week 16. Those who had a response entered the maintenance study and received 90mg of SC ustekinumab every 8 weeks (patients with a delayed response to ustekinumab). Patients who had a response to IV placebo at week 8 received SC placebo.[3, 4] These two groups of patients were considered as the non-randomised maintenance population and efficacy results were not reported in the key paper.[4]

Aminosalicylates and immunomodulators were continued at stable doses from the baseline of induction therapy until week 44 of maintenance therapy. Oral corticosteroids were maintained at a stable dose during the induction study and tapered when patients entered the maintenance study.[3, 4]

The primary outcome was clinical remission, at week 8 in the induction study and week 44 in the maintenance study. Clinical remission was defined as a total Mayo score of ≤2 and no sub-score >1.[4] At week 8, clinical remission was achieved by a significantly greater proportion of patients in

both the ustekinumab 6mg/kg and ustekinumab 130mg groups compared with those in the placebo group.[3, 4] At week 44, a significantly greater proportion of patients were in clinical remission in both the ustekinumab 12 weekly group and 8 weekly group compared with the placebo group.[3, 4] A hierarchical statistical testing strategy was applied in the study for key secondary outcomes, with no formal testing of outcomes after the first non-significant outcome in the hierarchy. All key secondary outcomes achieved statistical significance in favour of ustekinumab over placebo with the exception of maintaining clinical remission in those who were in clinical remission at baseline in the maintenance study (ustekinumab 8 weekly treatment group). Results for the primary and key secondary outcomes are included in Tables 2 and 3.

Table 2: Primary and key secondary outcomes at week 8 of the UNIFI induction study (primary analysis population).[3, 4]

	Ustekinumab IV 6mg/kg (licensed induction dose) (n=322)	**Ustekinumab IV 130mg (n=320)**	**Placebo (n=319)**
Clinical remission	15.5%	15.6%	5.3%
Difference versus placebo (95% CI, p value)	10.2% (5.6 to 14.8, p<0.001)	10.3% (5.7 to 14.9, p<0.001)	-
Endoscopic improvement	27%	26%	14%
Difference versus placebo (95% CI, p value)	13% (7.3 to 19, p<0.001)	12% (6.5 to 18, p<0.001)	-
Clinical response	62%	51%	31%
Difference versus placebo (95% CI, p value)	30% (23 to 38, p<0.001)	20% (12 to 27, p<0.001)	-
Baseline IBDQ Score	127	126	127
Change from Baseline in Total IBDQ Score	31	32	10
p value versus placebo	p<0.001	p<0.001	-
Histo-endoscopic mucosal healing*	18%	20%	8.9%
Difference versus placebo (95% CI, p value)	9.5% (4.5 to 15, p<0.001)	11% (6 to 17, p<0.001)	-

CI: Confidence interval, IBDQ: inflammatory bowel disease questionnaire, IV: intravenous *additional secondary outcome controlled for multiplicity

Table 3: Primary and key secondary outcomes at week 44 of the UNIFI maintenance study (primary analysis population: patients who had a response to IV ustekinumab in the induction study).[3, 4]

	Ustekinumab SC 90mg 12 weekly (n=172)	Ustekinumab SC 90mg 8 weekly (n=176)	Placebo (n=175)
Clinical remission	38%	44%	24%
Difference versus placebo (95% CI, p value)	14% (5.5 to 24, p=0.002)	20% (10 to 29, p<0.001)	-
Maintaining clinical response	68%	71%	45%
Difference versus placebo (95% CI, p value)	24% (14 to 33, p<0.001)	26% (17 to 36, p<0.001)	-
Endoscopic improvement	44%	51%	29%
Difference versus placebo (95% CI, p value)	15% (5.8 to 25, p=0.002)	22% (13 to 32, p<0.001)	-
Clinical remission and not receiving corticosteroids	38%	42%	23%
Difference versus placebo (95% CI, p value)	14% (5.5 to 24, p=0.002)	18% (9.3 to 28, p<0.001)	-
Clinical remission at baseline	n=40	n=38	n=45
Maintaining clinical remission	65% (26/40)	58% (22/38)	38%
Difference versus placebo (95% CI, p value)	28% (8 to 49, p=0.01)	20% (0 to 41, p=0.07)	-

CI: Confidence interval, SC: subcutaneous

Patient reported outcomes included change from baseline in total Inflammatory Bowel Disease Questionnaire (IBDQ) score, assessed as a major secondary outcome in the induction study (results in Table 2). The IBDQ is a disease-specific instrument and contains four components: bowel symptoms, systemic symptoms, emotional function, and social function. Total score ranges from 32 to 224 (higher scores indicating better health-related quality of life) and an increase of ≥16 points has been considered a clinically relevant improvement. Median IBDQ scores were similar at baseline across groups and at week 8 the median improvement from baseline was significantly greater in both ustekinumab groups compared with the placebo group.[3, 4] At Week 44, the median changes from maintenance baseline in the total IBDQ score favoured both ustekinumab groups compared with placebo (5.0 and 1.5 in the ustekinumab 8 weekly and 12 weekly groups, respectively, compared with -7.0 in the placebo group).[3]

Health-related quality of life was also assessed using the 36-item Short Form Health Survey (SF-36). At week 8, notably greater median increases in the physical component summary (PCS) and the mental component summary (MCS) scores and all 8 subscale scores of the SF-36 were observed in both ustekinumab groups compared with the placebo group. In addition, greater proportions of patients in both ustekinumab groups achieved a clinically meaningful improvement (≥5-point) from baseline in both PCS and MCS scores. At Week 8, median changes from baseline in the EuroQoL-5D Health Questionnaire (EQ-5D) index and the health state visual analogue scale were greater in both ustekinumab groups compared with the placebo group.[3]

The submitting company presented 12 network meta-analyses (NMA) comparing ustekinumab with vedolizumab, adalimumab, golimumab, infliximab, and tofacitinib. The NMA were conducted using data from the induction and maintenance phase of treatment in non-biologic failure patients and biologic failure patients with moderate to severe ulcerative colitis. Outcomes included clinical remission, clinical response, and mucosal healing (except for the biologic failure population in the maintenance phase). The results of the induction phase NMA were used to inform the economic base case. An NMA of safety, in both populations, was also performed using data from the induction phase and the reported outcomes were overall adverse events, serious adverse events, overall infections, and serious infections. Overall, there was variation in the results which sometimes favoured ustekinumab and in others favoured the comparators however all credible intervals overlapped, suggesting there is likely no difference between treatments.

Summary of evidence on comparative safety

The European Medicines Agency (EMA) concluded that overall no new serious safety signals had arisen for ustekinumab in patients with ulcerative colitis compared with use in Crohn's disease. However, due to the limited long-term safety data, the risk of adverse events such as serious infection and malignancy will be further characterised in additional studies.[3]

In the induction phase of UNIFI, after one dose of study treatment with an average follow-up of 8.6 to 8.7 weeks across groups. Adverse events were recorded in 41%, 51% and 48% of the ustekinumab 130mg, ustekinumab 6mg/kg and placebo groups respectively and serious adverse events were reported in 3.7%, 3.4% and 6.9% of the respective groups. Infections were reported in 16% of the ustekinumab groups and 15% of the placebo group.[4]

In the randomised population of the maintenance phase (patients who responded to the IV induction dose of ustekinumab), at an average follow-up of 42 weeks, adverse events were reported in 69%, 77% and 79% of the ustekinumab 90mg every 12 weeks, ustekinumab 90mg every 8 weeks and placebo groups respectively. Serious adverse events were reported in 7.6%, 8.5% and 9.7%and adverse events leading to discontinuation occurred in 5.2%, 2.8% and 11% of the respective groups.[4] Similar adverse event rates were observed in the non-randomised population (patients who responded to placebo and continued to receive placebo and patients who had a delayed response to ustekinumab and received 90mg every 8 weeks).[4]

In the randomised population of the maintenance phase, commonly reported adverse events included infections (34% in the ustekinumab 12 weekly group, 49% in the ustekinumab 8 weekly group, and 46% in the placebo group), nasopharyngitis (18%, 15%, and 16%), worsening of ulcerative colitis (11%, 10%, and 29%), and headache (6.4%, 10%, and 4.0%). Adverse events in the non-randomised population were generally consistent with the randomised population.[4] Four patients who received ustekinumab had potential opportunistic infections: cytomegalovirus colitis (two patients), legionella pneumonia (one patient) and concurrent ophthalmic and oral herpes simplex infection (one patient).[4]

The EMA noted that a higher standardised rate of malignancies was observed for ustekinumab in ulcerative colitis compared with epidemiological data from the Surveillance, Epidemiology, and End Results (SEER) database for other indications. Long-term safety of ustekinumab in patients with ulcerative colitis will be further characterised by a long term safety extension of the maintenance study and two prospective observational category 3 post authorisation safety studies as defined in the risk management plan.[3]

Summary of clinical effectiveness issues

Ulcerative colitis is a chronic inflammatory disease of the colon that follows a relapsing, remitting course with almost 70% of patients experiencing a flare every few months. Symptoms can be severe and negatively impact on quality of life. Patients commonly have diarrhoea, rectal bleeding, passage of mucus, abdominal pain, urgency, and may experience fatigue, fever, weight loss, dehydration and potentially fatal fulminant colitis. Ulcerative colitis is also associated with an increased risk of colorectal cancer. There is currently no pharmacological cure for ulcerative colitis. The aim of treatment is to induce and maintain disease remission to improve quality of life, reduce the need for long-term corticosteroids, reduce in the need for colectomy and minimise cancer risk.[3, 5]

Treatment options for the indication under review include TNF inhibitors (adalimumab, infliximab, and golimumab), tofacitinib, a Janus kinase inhibitor, or vedolizumab, an α4β7 integrin antagonist. Patients may not respond to treatment initially or may lose response over time. Colectomy is an option for refractory ulcerative colitis, however is associated with significant adverse events and complications.[3, 5] Clinical experts consulted by SMC considered that ustekinumab fills an unmet need in this therapeutic area, namely patients who are intolerant to, have no response to or lose response to currently available treatments.

In the UNIFI induction study, at week 8, clinical remission was achieved by a significantly greater proportion of patients in both ustekinumab groups compared with those in the placebo group. The difference of around 10% between the ustekinumab groups and placebo group is fairly small however the EMA considered that this was a very demanding outcome and therefore the difference was clinically relevant. At week 44 in the maintenance study, a significantly greater proportion of patients were in clinical remission in both the ustekinumab 12 weekly and 8 weekly groups compared with the placebo group. Both ustekinumab groups were superior to placebo for maintaining clinical response, endoscopic improvement and steroid-free clinical remission, assessed as secondary outcomes. Results favoured ustekinumab over placebo in patients who were previous biologic and non-biologic failures.[3, 4] The maintenance study only included patients who had responded to ustekinumab in the induction study, therefore the benefit observed is only for patients who had an initial response. The proportion of patients who had clinical remission would be different if all patients had entered maintenance regardless of the clinical outcome in the induction study.

Current EMA guidance states that the co-primary outcomes should be the proportion of patients in symptomatic remission and the proportion of patients with endoscopic remission which should include no rectal bleeding (subscore 0). For maintenance studies this should be achieved without steroids.[6] The primary outcome in UNIFI does not match these recommendations. However, the EMA noted that, when also considering the United States (US) definition of clinical remission (which included rectal bleeding score of 0), assessed as a primary outcome, and the secondary outcomes (particularly steroid-free remission), the UNIFI studies demonstrated clinically meaningful benefits for both endoscopic and symptomatic remission. The EMA therefore concluded the efficacy of ustekinumab had been demonstrated in both the induction and maintenance studies, even in heavily pre-treated patients.[3]

Approximately 84% of patients in the induction study had moderate disease (Mayo score 6 to 10) and only around 15% had severe disease (Mayo score >10). The EMA noted that efficacy in severely treatment refractory patients (refractory to both TNF inhibitors and vedolizumab) was based on small numbers and the study was not powered to demonstrate statistically significant results in this patient group. Information is included in the SPC noting the lack of evidence. Study treatment was discontinued in almost double the number of patients in the placebo group than in the ustekinumab groups combined. This was mainly due to lack of efficacy, worsening of ulcerative colitis and failure to achieve partial Mayo response at week 16 which are likely to be linked to the lack of effect of placebo. Patients received up to 52 weeks of treatment with ustekinumab which was sufficient to demonstrate efficacy however ulcerative colitis is a chronic condition and patients may stop responding to treatment over time.[3]

There are no data comparing ustekinumab with relevant comparators. The absence of direct comparative evidence was addressed via the indirect treatment comparisons. However the analyses had a number of limitations: there was heterogeneity in patient characteristics including prior treatment, maintenance study design and in the results reported for the control groups (placebo); the event counts were low for clinical remission, especially in the biologic failure population, which lead to uncertainty in some of the treatment effects reported in the analyses; comparisons made in the majority of the NMA were based on a single trial, therefore a random effects model could not be applied. Overall, despite the limitations, the results of the NMA suggest that ustekinumab is likely to be comparable to vedolizumab, adalimumab, golimumab, infliximab, and tofacitinib in both the induction and maintenance phases.

Clinical experts consulted by SMC considered that the place in therapy of ustekinumab is likely to be in patients who have failed treatment with TNF inhibitors. Ustekinumab maintenance treatment is administered by subcutaneous injection every 8 or 12 weeks which may have less impact on the patient and service than alternative biologic medications that are administered intravenously or those requiring more frequent administration.

Summary of comparative health economic evidence

The submitting company provided two analyses evaluating ustekinumab for the treatment of adult patients within its licensed indication. A cost-minimisation approach was used as the main evidence within the submission, on the assumption of equivalent clinical effectiveness to vedolizumab, supplemented by a cost-utility analysis (CUA) which included pairwise comparisons with vedolizumab, infliximab (and biosimilars), adalimumab (and biosimilars). Clinical expert input suggested that vedolizumab may be the main comparator for this submission.

For the cost-minimisation analysis (CMA), a simple cost comparison was used, evaluating the total costs of treatment (medicines acquisition costs plus administration costs) over a five-year time horizon. An assumption of clinical equivalence to vedolizumab was taken in the CMA and no clinical or patient-reported inputs were applied. The CMA assumed that the cost of intravenous delivery of vedolizumab is equivalent to the Scottish tariff of 'inflammatory bowel disease length of stay 1 day or less' (FZ37F). An assumption of like-for-like dosing was utilised, making comparisons between the longer and shorter dosing frequencies of the two medicines (high dose: high dose and low dose: low dose).

The CUA structure was largely consistent with previous SMC submissions, utilising a short-term decision tree structure to model induction treatment, which determined the distribution of patients across the subsequent Markov model representing maintenance treatment. Patients could receive surgery following loss of response, and transition to an absorbing death state at any time. A perspective of NHS Scotland and a lifetime horizon were used.

The CUA utilised two separate approaches: for the induction phase, a fixed-effects network meta-analysis described in the clinical effectiveness section was used to derive odds ratios for each biologic within the comparison. For the maintenance phase, response rates were directly obtained from clinical trials of each medicine and used unadjusted within the model. Utility estimates and health state costs were obtained from published literature.[7,8]

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. A PAS discount is in place for vedolizumab and this was included in the results used for decision-making by using estimates of the comparator PAS price.

The base case and key scenario analysis results of the CMA are shown in Table 4. Due to the limitations with the cost-utility analysis (discussed below), the results from this supplementary analysis were not considered reliable for decision-making and therefore SMC used the CMA as the primary source of cost-effectiveness evidence.

The results presented versus vedolizumab do not take account of the PAS for ustekinumab or the PAS for vedolizumab but these were considered in the results used for decision-making. 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.

Table 4: Base case analysis: CMA results at list prices

	Incremental costs (ustekinumab versus vedolizumab)
Base case	
Higher dosing frequency[1]	-£91,307
Lower dosing frequency[2]	-£34,084
Scenario: 50% reduction in administration costs	
Higher dosing frequency[1]	-£73,656
Lower dosing frequency[2]	-£25,112
[1]Ustekinumab 90mg q8w versus vedolizumab 300 mg q4w [2]Ustekinumab 90mg q12w versus vedolizumab 300mg q8w; PAS: patient access scheme	

Some limitations exist with the submission:

CMA: It is unclear whether the unit cost applied for administration of vedolizumab (covering one-day procedures for inflammatory bowel disease) is appropriate for routine intravenous infusion. However, if costs of intravenous administration are reduced by 50%, the results remain consistent with the base case.

- CUA: The main issue with the cost-utility analysis was the reliance on indirect comparisons which have significant limitations, both in terms of the induction network meta-analyses and additional use of direct unadjusted data in the maintenance phase. These created significant concerns regarding the reliability of the estimates informing the relative effectiveness (and thus predicted QALY gains) of ustekinumab with key comparators. Any estimates produced by the CUA were considered to be unreliable.

Despite these issues, the economic case was demonstrated.

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

Summary of patient and carer 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 3.97% pharmaceutical company funding in the past two years, including from the submitting company.

- The symptoms of ulcerative colitis, and their unpredictable nature can have a profound and devastating impact on all aspects of a person's life. Frequent diarrhoea, abdominal pain and

fatigue, anaemia, extra-intestinal manifestations such as joint, skin and eye problems, and the side effects of medications, all affect an individual's ability to work, study, socialise, participate in leisure activities or have intimate relationships. Emotional well-being can be significantly affected, stigma and lack of understanding of the condition exacerbate the impact.

- Current treatments available in NHS Scotland remain far from optimal for patients, a substantial number of whom experience lack of response (primary or secondary) and/or adverse reactions to medical treatments and may face the prospect of surgery with considerable anxiety.

- Ustekinumab would offer an important additional treatment option for those patients for whom conventional therapies have failed, who have lost response to anti-TNF therapies, or for whom anti-TNF therapies are contraindicated. It may help to delay or prevent surgery.

While the initial dose of ustekinumab is given intravenously, further doses are subcutaneous. Patients commented that this was convenient for them, reducing the amount of time they spent at hospital and reducing costs involved in travel and time away from work and family.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published NICE Clinical Guideline 130, Ulcerative colitis: management in May 2019.[9] The current NICE guidance make recommendation based on the severity of the condition. The guidance highlights that the use of biologics and Janus kinase inhibitors for moderately to severely active ulcerative colitis (all extents of disease) should be informed by the technology assessments for specific agents: infliximab, adalimumab, golimumab, vedolizumab, and tofacitinib. This guidance pre-dates the availability of ustekinumab for ulcerative colitis.[9]

The British Society of Gastroenterology produced consensus guidelines on the management of inflammatory bowel disease in adults in 2019.[10] This guideline recommends that in patients with ulcerative colitis who have failed treatment with high dose mesalazine, treatment options include thiopurine, anti-TNF therapy, vedolizumab or tofacitinib. It does not recommend methotrexate. Vedolizumab and tofacitinib are recommended when anti-TNF treatment has failed. This guideline was produced prior to ustekinumab receiving a license from the EMA for ulcerative colitis.[10]

The European Crohn's and Colitis Organisation (ECCO) published the Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management in 2017.[11] This guidance recommends that patients with steroid-dependent disease should be treated with a thiopurine, anti-TNF (preferably combined with thiopurines, at least for infliximab), vedolizumab, or methotrexate. In case of treatment failure, second-line medical therapy with an alternative anti-TNF, vedolizumab, or colectomy should be considered.[11]

Additional information: comparators

Vedolizumab, adalimumab, infliximab, golimumab, or tofacitinib.

Additional information: List price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Ustekinumab	**IV induction: approximately 6mg/kg body weight. SC maintenance starting at week 8: 90mg every 12 weeks, increased to every 8 weeks if needed.**	**First year: 17,176 Subsequent years: 8,588**

IV: intravenous, SC: subcutaneous. Costs from BNF online on 16 December 2019. Costs do not take any patient access schemes into consideration. Doses based on 12 weekly maintenance dosing and assuming weight 70kg. Cost will be increased if 8 weekly dosing is required.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be approximately 4,200 non-biologic failure patients and 2,000 biologic failure patients to which confidential estimates of treatment uptake were applied**.**

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

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This assessment is based on data submitted by the applicant company up to and including 14 February 2020.

**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*

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 medicine 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 NHSScotland 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 NHSScotland 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.