

**ustekinumab, 45mg solution for injection (Stelara®) No. (572/09)**  
**Janssen-Cilag Ltd**

15 January 2010

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 restricted use within NHS Scotland for the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and psoralen and UVA treatment (PUVA).

Significantly more patients treated with ustekinumab achieved at least 75% improvement in their Psoriasis Area and Severity Index (PASI) score at week 12, compared with those treated with a tumour necrosis factor alpha antagonist.

Continued treatment should be restricted to patients who achieve a PASI 75 response within 16 weeks.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of ustekinumab. This SMC advice is dependent upon the continuing availability of the patient access scheme in NHS Scotland.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**

**Indication**

For the treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate and psoralen and UVA treatment (PUVA).

**Dosing information**

A dose of 45mg (90mg for patients with body weight >100kg) administered subcutaneously at weeks 0 and 4 and then every 12 weeks thereafter. In patients weighing >100kg, 45mg was also shown to be efficacious, however 90mg resulted in greater efficacy in these patients.

Consideration should be given to discontinuing treatment in patients who have shown no response after up to 28 weeks of treatment.

Ustekinumab should be used under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis.

**Product availability date**

22 January 2009

**Summary of evidence on comparative efficacy**

Psoriasis is a chronic, systemic, autoimmune disease involving abnormal regulation of activated T cell interactions with antigen presenting cells and overproduction of pro-inflammatory cytokines. Ustekinumab is a fully humanised monoclonal antibody and is the first treatment to specifically target interleukin (IL)-12 and IL-23. It binds to the p40 subunit common to both these cytokines, preventing binding to receptors on the surface of T cells thereby disrupting differentiation, clonal expansion and the inflammatory cascade.

The evidence supporting this submission comes from the 12-week data of one active-controlled study and from the 76-week and 52-week data of two placebo-controlled studies of ustekinumab in patients with moderate to severe psoriasis.

A multicentre, randomised, active-controlled, investigator-blinded study recruited adults with a diagnosis of plaque psoriasis  $\geq 6$  months, a psoriasis area severity index (PASI)  $\geq 12$  and body surface area (BSA) involvement  $\geq 10\%$ , who were candidates for phototherapy or systemic psoriasis treatment and had failed to respond to, or had a contraindication to, or were intolerant of ciclosporin, methotrexate or PUVA. Patients were naïve to study drug treatment. After a screening period, 903 patients were randomised in a 3:5:5 ratio to receive subcutaneous ustekinumab 45mg, ustekinumab 90mg (at weeks 0 and 4) or etanercept 50 mg twice weekly until week 12. All patients were unblinded to study drug assignment but those randomised to ustekinumab were blinded to the dose.

Patients had a median age of 45 years, 68% were male, and had a median psoriasis duration of 17 years, median BSA involvement of 20%, median PASI score of 17; 43% had a physician's global assessment (PGA) of 'marked' or 'severe'. PASI scores range from 0 to 72, with higher scores representing more severe disease. Both PASI and PGA grade lesions according to the degree of erythema, induration and scaling. PASI also takes into account the affected body area.

The primary endpoint of  $\geq 75\%$  improvement in clinical severity (PASI 75) at Week 12 was achieved in significantly more patients treated with ustekinumab 45mg and 90mg, (68% and 74% respectively) than with etanercept, (57%). When considering some secondary endpoints, treatment with either dose of ustekinumab also produced significant improvements in the proportion of patients with a PGA score of 'cleared'/'minimal' and PASI 90 response (at least 90% improvement in clinical response) when compared with etanercept.

**Table 1 Active comparator study: clinical outcomes at 12 weeks**

	Ustekinumab 45mg (weeks 0 & 4)	Ustekinumab 90mg (weeks 0 & 4)	Etanercept 50mg twice weekly
Number of patients randomised	209	347	347
<b>Primary outcome</b> PASI 75 response % (n)	68% (141)	74% (256)	57% (197)
<b>Secondary outcomes</b> PGA cleared/minimal % (n)	65% (136)*	71% (245)*	49% (170)
PASI 90 response % (n)	36% (76)*	45% (155)*	23% (80)

\* significant difference versus etanercept; PGA = Physician Global Assessment; PASI = Psoriasis Area & Severity Index

Two similar ongoing, randomised, double-blind, placebo-controlled studies, with virtually the same inclusion criteria as the active-controlled study, initially randomised 766 and 1,230 patients equally to receive subcutaneous ustekinumab 45mg or 90mg (at weeks 0 and 4 and every 12 weeks thereafter) or placebo at weeks 0 and 4. Randomisation was stratified by investigational site, weight ( $\leq 90$  kg or  $>90$  kg), and whether the patient had an inadequate response, intolerance or contraindication to  $<3$  or  $\geq 3$  conventional systemic therapies.

Both placebo-controlled studies comprised four distinct study periods over approximately five years. Results are available for the first three periods.

- 12-week placebo-controlled period
- 28-week (16-week in the second study) placebo crossover and active treatment period
- a randomised withdrawal period beginning at week 40 (first study); a 24-week dose optimisation period beginning at week 28 (second study)
- a long-term extension period

In the first placebo-controlled study, patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45mg or 90mg) at Weeks 12 and 16 followed by dosing every 12 weeks. Patients initially randomised to ustekinumab who achieved PASI 75 at both weeks 28 and 40 were re-randomised to receive ustekinumab every 12 weeks (at their original dose) or placebo (withdrawal of therapy). Patients who were re-randomised to placebo at Week 40 re-initiated ustekinumab at their original dose when they experienced  $\geq 50\%$  loss of the PASI improvement obtained at week 40. All patients were followed for up to 76 weeks following first administration of study treatment.

In the second placebo-controlled study, patients randomised to ustekinumab received 45mg or 90mg doses at Weeks 0 and 4 followed by an additional dose at 16 weeks. Patients randomised to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16. At week 28 partial responders (patients who had initially been assigned to receive ustekinumab who had achieved  $\geq 50\%$  but  $<75\%$  improvement) were re-randomised to continue receiving study drug every 12 weeks or to intensified dosing every 8 weeks. Patients not achieving PASI 50 at week 28 discontinued treatment and patients achieving PASI 75 at week 28 continued to receive study drug every 12 weeks.

The primary endpoint of PASI 75 response at Week 12 (intention to treat analysis) was met in both placebo-controlled studies: ustekinumab 45mg (67% and 67%), ustekinumab 90mg (66% and 76%) and placebo (3% and 4%), for the first and second studies respectively. Eighty-five per cent of the patients re-randomised to placebo who restarted their original ustekinumab treatment regimen after loss of  $\geq 50\%$  of PASI improvement regained PASI 75 response within 12 weeks after restarting therapy.

In both placebo-controlled studies ustekinumab, compared with placebo, produced significant improvements in the proportion of patients with PGA scored as 'cleared' or 'minimal', PASI 90 and PASI 50 responses. Significant improvements in quality of life, assessed by Dermatology Life Quality Index (DLQI - range 0 to 30 with lower scores indicating better quality of life), were demonstrated in patients receiving ustekinumab within the first month of treatment in both studies and were sustained for around six months.

With long-term treatment (up to 40 weeks) the response was durable. There was some evidence of the efficacy of re-treatment in patients who lost 50% of their PASI response on discontinuing therapy in the first placebo-controlled study. Relapse occurred within eight weeks of treatment withdrawal.

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

## **Summary of evidence on comparative safety**

In the 12-week comparative study similar proportions of patients in the ustekinumab 45mg, ustekinumab 90mg and etanercept treatment groups experienced adverse events (AEs), 66%, 68% and 69% respectively, and serious adverse events (SAEs) 1.9%, 1.2% and 1.2% respectively. AEs led to treatment discontinuation in 1.9% and 1.2% of patients in the ustekinumab 45mg and 90mg groups respectively, compared with 2.3% of patients treated with etanercept.

Injection site erythema was the most commonly reported event in the etanercept group and occurred more frequently than in the combined ustekinumab groups (15% versus 0.7%, respectively). This may be due to the more frequent dosing schedule of etanercept (twice weekly for 12 weeks) compared with ustekinumab (two injections per patient for the active comparator duration of the study).

The rates of infection or serious infection were similar between ustekinumab-treated patients and those treated with etanercept. No cases of active tuberculosis were reported.

There were 4 reports of malignancy in the ustekinumab groups; 3 (2 cutaneous, 1 systemic) in the 45mg group and 1 (cutaneous) in the 90mg group. One of these (a cutaneous cancer) was thought to be possibly related to the study drug. There were no reports of malignancy in the etanercept group.

Long-term safety data are limited.

## **Summary of clinical effectiveness issues**

In the only comparative study, ustekinumab improved psoriasis outcomes in significantly more patients than etanercept. This study differed from Scottish practice as the dose of the comparator, etanercept, was 50mg twice weekly, which is double that recommended for use in Scotland.

Only 53% of patients in the first and 61% of patients in the second placebo-controlled study were non-responsive, intolerant, or had a contraindication to other systemic therapy and therefore correspond to the licensed patient population. All three studies enrolled a higher proportion of male patients, a difference not seen in patients with psoriasis.

From analysis of response by dose and body weight, a patient weight above 100kg was identified as optimising the risk-benefit ratio for the use of the higher (90mg) dose of ustekinumab.

A mixed treatment comparison (MTC) conducted on the weight-based dosing results for ustekinumab to examine the relative efficacy of ustekinumab and comparators used methodology previously employed by the National Institute for Health and Clinical Excellence (NICE) in a Multiple Technology Appraisal of biological therapies for psoriasis. As the three ustekinumab studies did not use weight-based dosing, only sub-populations of these studies were analysed in the MTC and therefore the relative efficacy of these biological therapies in moderate to severe psoriasis remains unclear.

The long-term safety and efficacy of ustekinumab are as yet unknown. In the event of a significant adverse event the long half-life of the product is a potential disadvantage. The pharmacodynamic effects of ustekinumab are irreversible until plasma concentrations are very low and the function of the suppressed cell populations has recovered, which may be a period of months.

Ustekinumab has the advantage of less frequent dosing than the TNF-alpha antagonists.

## **Summary of comparative health economic evidence**

The manufacturer submitted a cost-utility analysis that compared ustekinumab to etanercept (continuous use or intermittent use), adalimumab, infliximab or “standard care”. Current treatment patterns are variable but the comparisons with etanercept were considered most relevant by SMC experts, and in particular, the comparison with etanercept 25mg used on a continuous basis. Costs and benefits were estimated over a 10-year time horizon using a model with many common elements to that developed for the NICE health technology assessment of etanercept and efalizumab for psoriasis (TA103, published in 2006).

Clinical evidence combined data from the ustekinumab clinical trials programme with randomised control trials of other biological treatments in a ‘mixed treatment comparison’. A drop-out rate for all active treatments of 20% per year was assumed, as in the earlier NICE appraisal. Utilities were estimated by the conversion of disease-specific measures into EQ5D states. Costs included the medicines used, administration and monitoring, and treatment of those who did not respond or stopped responding to treatment including occasional hospital admissions of 21 days.

The results indicated that the cost per QALY of ustekinumab against etanercept 25mg used continuously was £97,063 (based on incremental costs of £1,495 and incremental QALYs of 0.0154). Compared to etanercept 50mg used continuously the ICER was £127,267 (based on incremental costs of £1,018 and incremental QALYs of 0.008). In the comparison with etanercept 25mg used intermittently the ICER was £99,743 (based on incremental costs of £2,332 and incremental QALYs of 0.0233).

A Patient Access Scheme (PAS) was submitted by the manufacturer and assessed by the Transitional Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, the manufacturer will provide a second vial

of ustekinumab at no additional cost in those patients who require it (i.e. patients weighing over 100kg). It was assumed that only a proportion of patients treated would weigh over 100kg and thus require a second vial of ustekinumab. After integrating the PAS into the economic analysis, the results indicated that ustekinumab would dominate both etanercept 25mg continuous use (based on cost savings of £271 and incremental QALYs of 0.0154) and etanercept 50mg continuous use (based on cost savings of £758 and incremental QALYs of 0.008). Compared to etanercept 25mg used intermittently, the ICER was £23,920 (based on incremental costs of £557 and incremental QALYs of 0.0233).

The main concern about the economic analysis was that the mixed treatment comparison suggested a greater efficacy advantage for ustekinumab over etanercept than was seen in the randomised controlled trials where they were compared directly. The manufacturer explained that this was because the etanercept response in that randomised controlled trial was higher than had been observed in other clinical trials.

Overall, the economic case for use, subject to the availability of the PAS, was considered to have been made.

### **Summary of patient and public involvement**

Patient Interest Groups Submissions were received from:

- PSALV, Psoriasis Scotland
- Skin Care Campaign Scotland (SCCS)

### **Additional information: guidelines and protocols**

The British Association of Dermatologists published revised guidelines in 2009 for the use of biological therapies in psoriasis which states: In light of limited patient exposure, ustekinumab should be reserved for use in patients with severe psoriasis who fulfil the stated disease severity criteria AND where anti-TNF therapy has failed or is contra-indicated.

NICE Technology Appraisal Guidance No 103, published in July 2006, approving the use of etanercept (at a weekly dose of 50mg) in the treatment of adults with psoriasis is applicable in Scotland.

### **Additional information: comparators**

Relevant comparators are the tumour necrosis factor alpha antagonists: adalimumab, etanercept and infliximab.

## Cost of relevant comparators

Drug	Dose regimen	Cost of initial trial period for response * £	Annual maintenance cost
Ustekinumab	By subcutaneous injection, 45mg (or 90mg if body weight >100 kg) at weeks 0, 4, then every 12 weeks thereafter. Initial trial period = 28 weeks	6,441	9,304
Infliximab**	By intravenous infusion, 5 mg/kg at weeks 0, 2 and 6, then every 8 weeks thereafter.  Initial trial period = 14 weeks	5,035	10,910
Adalimumab	By subcutaneous injection, initially 80mg then 40mg every other week starting one week after the initial dose. Initial trial period =16 weeks	3,575	9,295
Etanercept	By subcutaneous injection, 25mg twice weekly or 50 mg once weekly. *** Initial trial period = 12 weeks#	2,145	9,295

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 29.06.09. \*As per Summary of Product Characteristics \*\* Calculations based on 70kg body weight. \*\*\* A higher licensed dose of etanercept is not included as it has not been recommended by NICE Technology Appraisal Guidance No 103, endorsed by NHS Quality Improvement Scotland. #Maximum licensed duration of etanercept is 24 weeks.

## Additional information: budget impact

The net budget impact for the NHS in Scotland was estimated by the manufacturer to be £2k in year 1 rising to £14k by year 5. Note that these figures are based on implementation of the patient access scheme. This assumes that only proportion a patients are over 100kg. The figures were based on an assumption that ustekinumab would replace existing anti-TNFs, taking patients from each of them according to their market share at present.

Most costs are for the medicines in the short-term so this is likely to reflect the manufacturer's estimate of the drugs budget impact as well.

The manufacturer assumed 9 patients in year 1 and 173 in year 5. The manufacturer assumed a market share of 1.6% in year 1 rising to 24.8% in year 5. This does seem plausible and may even be an underestimate, although much will depend on how the other manufacturers respond in terms of price reductions.

So long as one therapy is substituted for the other and the patient access scheme operates as predicted the net budget impact will be low. If having another option prolongs therapy there will be a greater net cost but this is difficult to predict with accuracy.

**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.*

*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 together with the SMC advice.*

*This assessment is based on data submitted by the applicant company up to and including 11 December 2009.*

*Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.*

*\*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/>*

*The undernoted references were supplied with the submission. The reference shaded grey is additional to those supplied with the submission.*

Leonardi CL, Kimball AB, Papp KA et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008;371(9625):1665-74.

Papp KA, Langley RG, Lebwohl M et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008;371(9625):1675-84.

Griffiths C, Strober BE, Van De Kerkhof P et al. A Phase 3, Multicenter, Randomized Study Comparing Ustekinumab and Etanercept for the Treatment of Moderate to Severe Plaque Psoriasis. European Academy of Dermatology and Venereology Annual Congress Paris, FP1336. 2008.

British Association of Dermatologists. Guidelines for Biological Interventions for Psoriasis 2009