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

Evidence review for Surrey Prescribing Clinical Network

Medicine and proposed indication	Ustekinumab for treating active psoriatic arthritis
Requested by	NICE technology appraisal guidance 340 Rapid review of technology appraisal guidance 313 Issued June 2015

SUMMARY

Clinical Effectiveness

NICE TA 340 states:

1.1 Ustekinumab is recommended as an option, alone or in combination with methotrexate, for treating active psoriatic arthritis in adults only when:

- treatment with tumour necrosis factor (TNF) alpha inhibitors is contraindicated but would otherwise be considered (as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis) or

- the person has had treatment with 1 or more TNF–alpha inhibitors.

Ustekinumab is recommended only if the company provides the 90 mg dose of ustekinumab for people who weigh more than 100 kg at the same cost as the 45 mg dose, as agreed in the patient access scheme.

1.2 Ustekinumab treatment should be stopped if the person's psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 24 weeks. An adequate response is defined as an improvement in at least 2 of the 4 criteria (1 of which must be joint tenderness or swelling score), with no worsening in any of the 4 criteria. As recommended in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, people whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response (see NICE technology appraisal guidance on ustekinumab for the treatment of adults with moderate to severe psoriasis).

Reproduced from the Summary of Appraisal Committee's Key Conclusions (section 4 page 39 of the full guidance) with reference to the section within the full guidance.
Full guidance available at: https://www.nice.org.uk/guidance/ta340

Availability, nature and quality of evidence.
Section 4.5, 4.7

The Committee noted that the evidence for the clinical effectiveness of ustekinumab had been taken from 2 randomised placebo-controlled trials (PSUMMIT 1 and 2). The Committee concluded that ustekinumab is clinically effective compared with conventional management, in both TNF-alpha inhibitor-naive and TNF-alpha inhibitor-exposed populations, but

acknowledged that there remains some uncertainty about the long-term effects of ustekinumab.

The Committee considered the clinical effectiveness of ustekinumab compared with TNF-alpha inhibitors in the TNF-alpha inhibitor-naive population. The Committee reviewed the findings of the company's mixed treatment comparison and discussed them with the clinical experts, and was aware of the limitations of the mixed treatment comparison. It concluded that ustekinumab appeared to be less effective than TNF-alpha inhibitors for PASI 75, PASI 90 and PsARC response, particularly for the joint outcome.

Uncertainties generated by the evidence.
Section 4.5, 4.6, 4.7, 4.8

The Committee considered that, although the effect of ustekinumab is likely to persist for up to 1 year, there is some uncertainty about this because in the trials people switched from placebo to ustekinumab at week 24.

It considered that the evidence on radiographic progression with ustekinumab should be interpreted with caution.

It also acknowledged that there remains some uncertainty about the long-term effects of ustekinumab.

The Committee was aware of the limitations of the mixed treatment comparison.

The Committee concluded that there is still uncertainty about the relative effectiveness of ustekinumab and TNF-alpha inhibitors in people who have previously had TNF-alpha inhibitors.

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?
Section 4.7, 4.8, 4.9

The Committee considered the clinical effectiveness of ustekinumab compared with TNF-alpha inhibitors in the TNF-alpha inhibitor-naive population. It concluded that ustekinumab appeared to be less effective than TNF-alpha inhibitors for PASI 75, PASI 90 and PsARC response, particularly for the joint outcome.

The Committee also considered the clinical effectiveness of ustekinumab compared with TNF-alpha inhibitors in the TNF-alpha inhibitor-exposed population. It was aware that there was limited clinical trial evidence in this setting. It understood that there is some evidence for the effectiveness of TNF-alpha inhibitors in the TNF-alpha inhibitor-exposed population, but that there was not enough evidence to compare ustekinumab and TNF-alpha inhibitors. Evidence presented at a conference suggested that the effectiveness of Ustekinumab measured using the American College of Rheumatology (ACR) criteria may decrease with increasing numbers of prior TNF-alpha inhibitors.

The Committee concluded that there is still uncertainty about the relative effectiveness of ustekinumab and TNF-alpha inhibitors in people who have previously had TNF-alpha inhibitors.

The Committee also considered whether there may be any variation in clinical effectiveness depending on the reason for withdrawal of the first TNF-alpha inhibitor but it acknowledged that there was not enough evidence for this aspect to be considered further.

The Committee acknowledged that there is no clear evidence to support the use of a strict weight-based dosing strategy.
Estimate of the size of the clinical effectiveness including strength of supporting

evidence.
Section 3.3, 4.5

In both PSUMMIT 1 and 2, ustekinumab was associated with statistically significantly higher rates of ACR 20 response at week 24 than placebo. ACR 20 response rates in PSUMMIT 1 were 46.0% and 22.8% for ustekinumab 45 mg and 90 mg pooled, and placebo respectively ($p<0.0001$).

The Committee concluded that ustekinumab is clinically effective compared with conventional management, in both TNF-alpha inhibitor-naive and TNF-alpha inhibitor-exposed populations, but acknowledged that there remains some uncertainty about the long-term effects of ustekinumab.

Safety

Adverse reactions:

N/A (The Committee made no specific conclusions about adverse reactions.)

The patient expert highlighted that people with psoriatic arthritis often have concerns about the long-term safety of treatments for this condition. The Committee was aware of registers that collect evidence on the long-term treatment outcomes with TNF-alpha inhibitors for rheumatoid arthritis and psoriasis. The patient expert and the clinical experts emphasised the importance of collecting long-term data on psoriatic arthritis specifically. The Committee concluded that long-term evidence on the effectiveness and safety of biological treatments for psoriatic arthritis would be valuable.

Patient factors

The Committee heard from the clinical experts that there is a group of people with psoriatic arthritis for whom TNF-alpha inhibitors are not suitable, because of contraindications such as heart failure or demyelination, or because of failure of TNF-alpha inhibitors as a class. For these people there is a considerable unmet need.

The Committee understood that this affects a number of people and that for people in this situation there are no effective treatment options. The clinical experts considered that ustekinumab has the potential to offer an innovative treatment option to fulfil this need.

The Committee acknowledged that this represents a distinct group with an important unmet need that warrants additional consideration. During consultation, the Committee heard from a company that manufactures a TNF-alpha inhibitor that the contraindications for ustekinumab and TNF-alpha inhibitors are relatively similar. It therefore considered that the number of people who had not had TNF-alpha inhibitor therapy (that is, who were TNF-alpha inhibitor-naive), for whom TNF-alpha inhibitors as a class were contraindicated and for whom ustekinumab might be appropriate was unknown but may be relatively small.

The Committee concluded that conventional management would be an appropriate comparator in people for whom TNF-alpha inhibitors were contraindicated and in people whose condition failed to respond to TNF-alpha inhibitors as a class.

Cost implications

The list price for ustekinumab is **£2147 per 45-mg vial** (excluding VAT; British National Formulary online [accessed September 2015]).

The recommended dose of ustekinumab is an initial dose of 45 mg, followed by a dose 4 weeks later and further doses every 12 weeks thereafter. A dose of 90 mg may be used in people with a body weight over 100 kg.

The summary of product characteristics notes that consideration should be given to stopping

treatment in people whose psoriatic arthritis has shown no response after up to 28 weeks of treatment.

The average annual acquisition cost for ustekinumab 45 mg is £10,735 in the first year and £9304 per year thereafter.

The company has agreed a patient access scheme with the Department of Health, in which the company provides the 90-mg dose (2 vials) at the same cost as the 45-mg dose (1 vial), for people who weigh more than 100 kg and need the higher dose.

The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Relevant guidance / reviews

Ustekinumab for treating active psoriatic arthritis
NICE technology appraisal guidance 340
https://www.nice.org.uk/guidance/ta340

Likely place in therapy relative to current treatments

The Committee considered the likely place of ustekinumab in managing psoriatic arthritis. It heard from the clinical experts that if ustekinumab were to be used in people with prior TNF-alpha inhibitor exposure, it might be used after 1, 2 or more TNF-alpha inhibitors, depending on person-specific factors such as the reason for withdrawing the previous TNF-alpha inhibitor and individual preferences.

For example, if the previous TNF-alpha inhibitor had no effect or caused class-related adverse reactions, ustekinumab may be used in preference to another TNF-alpha inhibitor, whereas if the previous TNF-alpha inhibitor loses efficacy over time, another TNF-alpha inhibitor might be chosen before ustekinumab.

Recommendation to PCN

RED – Payment by Results excluded (PbRe).

In line with NICE TA 340, Ustekinumab is recommended as an option, alone or in combination with methotrexate, for treating active psoriatic arthritis in adults only when:

- treatment with tumour necrosis factor (TNF) alpha inhibitors is contraindicated but would otherwise be considered (as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis and golimumab for the treatment of psoriatic arthritis) or

- the person has had treatment with 1 or more TNF–alpha inhibitors.

Ustekinumab is recommended only if the company provides the 90 mg dose of ustekinumab for people who weigh more than 100 kg at the same cost as the 45 mg dose, as agreed in the patient access scheme.

Ustekinumab treatment should be stopped if the person's psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 24 weeks.

Notification of treatment initiation will be made through Blueteq tick box forms as per usual for funding PbRe drugs.

Medicine details	
Name and brand name	Ustekinumab (Stelara®, Janssen-Cilag Ltd) 45mg solution for injection in pre-filled syringe.
Licensed indication, formulation and usual dosage	Plaque psoriasis: Ustekinumab is indicated 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 (MTX) or PUVA (psoralen and ultraviolet A). Paediatric plaque psoriasis: Ustekinumab is indicated for the treatment of moderate to severe plaque psoriasis in adolescent patients from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Psoriatic arthritis (PsA): Ustekinumab, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Posology: Plaque psoriasis: The recommended posology of ustekinumab is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment. Patients with body weight > 100 kg For patients with a body weight > 100 kg the initial dose is 90 mg administered subcutaneously, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. In these patients, 45 mg was also shown to be efficacious. However, 90 mg resulted in greater efficacy. Paediatric plaque psoriasis (12 years and older) The recommended dose of ustekinumab is based on body weight is shown in the SPC. Ustekinumab should be administered at Weeks 0 and 4, then every 12 weeks thereafter. Psoriatic arthritis (PsA): The recommended posology of ustekinumab is an initial dose of 45 mg administered subcutaneously, followed by a 45 mg dose 4 weeks later, and then every 12 weeks thereafter. Alternatively, 90 mg may be used in patients with a body weight > 100 kg. Consideration should be given to discontinuing treatment in patients who have shown no response up to 28 weeks of treatment.
Summary of mechanism of action, and relevant pharmacokinetics	Ustekinumab is a human monoclonal antibody that acts as a cytokine inhibitor through targeting interleukin-12 (IL-12) and interleukin-23 (IL-23). It prevents these cytokines binding to the interleukin-2Rß1 receptors on natural killer cells, antigen-presenting cells or T-cells, and thus prevents subsequent receptor signalling

	and activation of the receptor-bearing cell (Ustekinumab SPC). It is administered by subcutaneous injection.
Important drug interactions	Live vaccines should not be given concurrently with ustekinumab. No interaction studies have been performed in humans. In the population pharmacokinetic analyses of the phase III studies, the effect of the most frequently used concomitant medicinal products in patients with psoriasis (including paracetamol, ibuprofen, acetylsalicylic acid, metformin, atorvastatin, levothyroxine) on pharmacokinetics of ustekinumab was explored. There were no indications of an interaction with these concomitantly administered medicinal products. The basis for this analysis was that at least 100 patients (> 5% of the studied population) were treated concomitantly with these medicinal products for at least 90% of the study period. The pharmacokinetics of ustekinumab was not impacted by concomitant use of MTX, NSAIDs and oral corticosteroids, or prior exposure to anti-TNFα agents, in patients with psoriatic arthritis. The results of an in vitro study do not suggest the need for dose adjustments in patients who are receiving concomitant CYP450 substrates. In psoriasis studies, the safety and efficacy of ustekinumab in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab.
Monitoring requirements	Ustekinumab is for subcutaneous injection. After proper training in subcutaneous injection technique, patients or their caregivers may inject ustekinumab if a physician determines that it is appropriate. However, the physician should ensure appropriate follow-up of patients. The summary of product characteristics lists the following common adverse reactions for ustekinumab: dental and upper respiratory tract infections,nasopharyngitis, dizziness, headache, oropharyngeal pain, diarrhoea, nausea, pruritus, back pain, myalgia, arthralgia, fatigue, injection-site erythema and injection-site pain. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Prescribing considerations	Red - PbRe
Other considerations	The ERG identified a number of limitations in the evidence available from the PSUMMIT studies. The switch from placebo to ustekinumab at weeks 16 and 24 provides a short-term comparison for a chronic condition such as psoriatic arthritis.

Potential patient group (if appropriate to include)	
Brief description of disease	Psoriatic arthritis is a type of arthritis that develops in some people with psoriasis. It typically causes affected joints to become inflamed, stiff and painful and can affect any joint in the body, but the condition often affects joints including the hands, feet, knees, neck, spine and elbows. Between one and two in every five people with psoriasis will develop psoriatic arthritis. It usually develops within 10 years of psoriasis being diagnosed, although some people may experience problems with their joints before they notice any symptoms affecting their skin. Like psoriasis, psoriatic arthritis is thought to occur as a result of the immune system mistakenly attacking healthy tissue, but it is not clear why some people with psoriasis develop psoriatic arthritis and others do not. The Committee understood that psoriatic arthritis is a lifelong condition that has a serious impact on people's quality of life. It heard from the patient expert that psoriatic arthritis can develop at a young age, and affects all aspects of a person's life including education, work, self-care, and social and family life. The Committee heard from the patient expert that skin symptoms can have a major psychological impact, and that the joint symptoms have an even greater impact on the psychological and functional aspects of living with this chronic condition. The Committee recognised the potential value of additional treatment options for people with psoriatic arthritis.
Potential patient numbers per 100,000	Ustekinumab is innovative for patients for whom a TNF-alpha inhibitor is contraindicated because it potentially fulfils an important unmet need. The number of people in this situation was unknown and may be very small.
Outcomes required	

Summary of current treatment pathway
Pathway for the use of biologics in psoriatic arthritis waiting to be ratified by clinicians.

Evidence review
Ustekinumab for treating active psoriatic arthritis NICE technology appraisal guidance 340 https://www.nice.org.uk/guidance/ta340

Health economic considerations	
Cost per year per patient	The average annual acquisition cost for ustekinumab 45 mg is £10,735 in the first year and £9304 per year thereafter.
Alternative treatments cost per patient per year	Adalimumab 40mg prefilled syringe = £352.14 Annual cost = £9155.64 Etanercept 25mg twice weekly or 50mg once weekly = £178.75 Annual cost = £9295 Golimumab 50mg or 100mg = £763.97 Annual cost = £9155.64 The use of infliximab is not supported in the local pathway but it is noted that NICE TA199 (August 2010) does recommend the use of infliximab. NICE recommend: Treatment choice should be started with the least expensive drug (taking into account drug administration costs, required dose and product price per dose).
Other financial considerations (if relevant)	
Health economic data (if available)	

References

NICE TA 340

Date:

Prepared by: Tejinder Bahra
Declaration of interest: None

Reviewed by:

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
1	3.9.15	T.Bahra	Draft	

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

Comments on Evidence review for Surrey Prescribing Clinical Network

Please include any comments you have answers to any questions asked as well as any additional references you feel may need to be included in the review. If there are any other of your colleagues that you feel we need to engage with please also let us know their names and where/how they can be contacted.

Medicine and proposed indication	
Prepared by	Name, designation and organisation
Comments on evidence review	
Additional evidence and references for consideration	Include any additional evidence and references you would like to submit for inclusion in the evidence review
Specific clinical questions	Specific questions arising from review
Other colleagues who should be contacted	Include name, designation and contact details of any other colleagues who should be consulted about this evidence
Declaration of interests	For example – any teaching, training, grants, consultancy, research funding, stock holding, nurse funding, equipment

Signature …….. Date ……