NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using adalimumab, etanercept and ustekinumab in the NHS in England. The appraisal committee has considered the evidence submitted and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on adalimumab, etanercept and ustekinumab. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using adalimumab, etanercept and ustekinumab the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 7 April 2017

Second appraisal committee meeting: 20 April 2017

Details of membership of the appraisal committee are given in section 7.

1 Recommendations

1.1 Adalimumab is recommended as an option for treating plaque psoriasis in children and young people aged 4 years or older, only if the disease:

- is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and
- has not responded to standard systemic therapy, such as ciclosporin, methotrexate or phototherapy, or it is contraindicated or not tolerated.

1.2 Etanercept is recommended as an option for treating plaque psoriasis in children and young people aged 6 years or older, only if the disease:

- is severe, as defined by a total PASI of 10 or more and
- has not responded to standard systemic therapy, such as ciclosporin, methotrexate or phototherapy, or it is contraindicated or not tolerated.

1.3 Ustekinumab is recommended as an option for treating plaque psoriasis in children and young people aged 12 years or older, only if the disease:

- is severe, as defined by a total PASI of 10 or more
- has not responded to standard systemic therapy, such as ciclosporin, methotrexate or phototherapy, or it is contraindicated or not tolerated and
- has not responded to at least 1 biological therapy or it is contraindicated or not tolerated.

1.4 Stop etanercept treatment at 12 weeks, and adalimumab and ustekinumab treatment at 16 weeks, if the psoriasis has not responded adequately. An adequate response is defined as a 75% reduction in the PASI score from the start of treatment.

1.5 When using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make the clinical adjustments they consider appropriate.

1.6 This guidance is not intended to affect the position of patients whose treatment with adalimumab, etanercept or ustekinumab was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop. This decision should be made jointly by the clinician and the child or young person or the child's or young person's parents or carers.

2 The technologies

Description of the technologies	Adalimumab (Humira, AbbVie) is a fully human immunoglobulin G1 monoclonal antibody that inhibits the activity of tumour necrosis factor alpha (TNF-alpha). Etanercept (Enbrel, Pfizer) is a recombinant human TNF-alpha receptor fusion protein that inhibits the activity of TNF-alpha. Ustekinumab (Stelara, Janssen) is a fully human monoclonal antibody that acts as a cytokine inhibitor by targeting interleukin−12 and interleukin−23.
Marketing authorisations	Adalimumab has marketing authorisation for treating 'severe chronic plaque psoriasis in children and adolescents from 4 years of age who have an inadequate response to or are inappropriate candidates for topical therapy and phototherapies'. Etanercept has a marketing authorisation for treating 'chronic severe plaque psoriasis in children and adolescents from the age of 6 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies'. Ustekinumab has a marketing authorisation for treating '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'.
Adverse reactions	For full details of adverse reactions and contraindications, see the summary of product characteristics for adalimumab, etanercept and ustekinumab.
Recommended doses and schedules	Adalimumab: initially 0.8 mg/kg every week (maximum per dose 40 mg) for 2 doses, then 0.8 mg/kg every 2 weeks (maximum per dose 40 mg). Etanercept: 0.8 mg/kg up to a maximum of 50 mg weekly for up to 24 weeks. Ustekinumab: 0.75 mg/kg for a body weight less than 60 kg; 45 mg for a body weight of between 60 kg and 100 kg; 90 mg for a body weight of above 100 kg at weeks 0 and 4, then every 12 weeks thereafter.
Prices	Costs may vary in different settings because of negotiated procurement discounts. The list prices (excluding VAT; 'British national formulary' [BNF] online, March 2017) are: £352.14 for 40 mg adalimumab in a prefilled pen or prefilled syringe; £178.75 for 50 mg etanercept in a prefilled pen or prefilled syringe; £2,147 for a 45 mg ustekinumab for a prefilled syringe.

3 Evidence

The appraisal committee (section 7) considered evidence from a number of sources. See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of adalimumab, etanercept and ustekinumab, having considered evidence on the nature of psoriasis and the value placed on the benefits of adalimumab, etanercept and ustekinumab by people with the condition, those who represent them, and clinical experts. The data on the clinical evidence was submitted by the assessment group, AbbVie (adalimumab) and Janssen (ustekinumab). The data on the cost-effectiveness evidence was submitted by the assessment group. It also took into account the effective use of NHS resources.

4.1 The committee heard from the patient and clinical experts about the experience of people with psoriasis. It heard that the disease results in itchy, dry, red, scaly plaques on the skin, which can be physically and psychologically debilitating. Psoriasis may be unpredictable, with flare-ups and remissions. The committee heard that, because psoriasis is visible, it can make children and young people feel isolated and lonely, which could lead to them losing self-confidence and avoiding social situations. The committee agreed that severe psoriasis reduces quality of life.

Treatment pathway

4.2 The committee heard from the clinical expert that the aim of treatment for people with psoriasis is to reduce the area of skin covered with psoriatic lesions and improve symptoms such as redness, flaking and itching. The committee was aware that, although there is a NICE guideline on psoriasis: assessment and management, treatment varies in practice. It heard from the clinical expert that children and young people have topical treatments first line. It heard that, if there is an inadequate response to treatment or if it is not tolerated or contraindicated, they can have systemic non-biological therapies (such as methotrexate, ciclosporin and phototherapy) second line. Clinicians then offer children and young people biological therapies or best supportive care third line. The clinical expert

informed the committee that, if the disease no longer responds to a biological treatment, clinicians offer patients another biological therapy. The committee was aware that if patients could not have biological therapy they would have best supportive care, which would be non-biological systemic treatment. These treatments can be associated with frequent hospital visits for monitoring or treatment administration that can be inconvenient. These treatments can also be associated with adverse effects, for example, people who have phototherapy have an increased risk of developing skin cancer. The committee understood from the clinical expert that biological treatments have had a positive effect on patients over recent years because there is no longer a need to be hospitalised for long periods for treatment or monitoring. The committee concluded that it is valuable to have a range of biological treatment options that have different mechanisms of action.

Position of technologies in the treatment pathway and comparators

4.3 The committee was aware that the marketing authorisations were different for adalimumab, etanercept and ustekinumab (see section 2). It was aware that adalimumab could be given as an alternative to non-biological systemic therapies but heard from the clinical expert that in clinical practice all 3 drugs are used as third line after topical therapies, phototherapy and non-biological systemic agents. It heard however, that patients and clinicians would welcome the opportunity to offer biologicals earlier in the treatment pathway. The committee concluded that the most appropriate comparator for adalimumab as a second-line treatment was non-biological systemic therapy (such as methotrexate). It also concluded that the most appropriate comparators for adalimumab, etanercept and ustekinumab as third-line treatment were each other and best supportive care, and that this was the point at which biologicals would most likely be used in the NHS.

Clinical effectiveness

4.4 The committee considered the randomised controlled trial evidence for adalimumab, etanercept and ustekinumab submitted by the companies and reviewed by the assessment group:

- M04-717 compared adalimumab with methotrexate in children and young people (n=114) aged 4 years to 17 years. At 16 weeks adalimumab had improved Psoriasis Area and Severity Index 75 (PASI 75; a 75% reduction in PASI response) more than methotrexate (relative risk [RR] 1.79, 95% confidence interval [CI] 1.04 to 3.06).
- 20030211 compared etanercept with placebo in children and young people (n=211) aged 4 years to 17 years. At 12 weeks, etanercept had improved PASI 75 more than placebo (RR 4.95, 95% CI 2.84 to 8.65).
- CADMUS compared ustekinumab with placebo in children and young people (n=110) aged 12 years to 17 years. At 12 weeks, ustekinumab had improved PASI 75 more than placebo (RR 7.5, 95% CI 2.9 to 19.1).

Generalisability of the clinical trials to clinical practice

4.5 The committee considered the severity of psoriasis and the way it was defined in clinical practice and in the trials. It heard from the clinical experts that clinicians use both the PASI and the Children's Dermatology Life Quality Index (CDLQI; a questionnaire designed for use in children aged 5 years to 16 years) when monitoring disease and choosing who to offer biological therapies. The committee noted that percentage reduction in PASI score was the primary end point in M04-717 and 20030211, and a secondary end point in CADMUS. It heard from the clinical expert that a 75% reduction in PASI (PASI 75) is a broadly used assessment method in children and young people. The committee agreed that the appropriate outcomes were captured in the trials. The committee concluded that PASI was a relevant measure used in clinical practice in the NHS and that PASI 75 was a clinically relevant definition of response to treatment.

4.6 The committee discussed the baseline characteristics of the patients in the trials:

- Severity: the committee noted that the definition of severity varied between trials (notably, the inclusion criteria differed). It heard from the clinical expert that in practice clinicians use the definitions outlined in existing NICE guidance for biological treatments in adults. It heard that that 'severe' disease is generally defined as a PASI of 10 or more. The committee noted that the trials mostly used a PASI at or above a score of 10.
- Age: the committee noted that the mean age between the trials differed. It understood that this reflected the marketing authorisation for each technology and that the assessment group accounted for these differences in its network meta-analysis (see section 4.9).

The committee heard from clinical experts that the trials broadly reflected children and young people with severe psoriasis in the NHS. It agreed that ‘severe’ disease should be defined as a PASI of 10 or more. It concluded that the clinical trial evidence was appropriate for decision-making and generalisable to NHS practice in England.

Network meta-analysis results

4.7 The committee heard from the assessment group that it was not possible to connect the interventions and comparators together using direct evidence from children and young people alone because the trials did not use a common comparator. The assessment group therefore presented 2 analyses, one using the minimal amount of adult data needed to connect the network and the other using all adult data available. The committee understood that the assessment group’s preferred analysis included all available adult data, because of the lack of evidence in children and young people. The committee understood that the assessment group adjusted for differences in population characteristics and placebo response rates because they differed between trials and

between children and adults. It agreed with the assessment group that all available adult evidence should be included in the network, and that it was appropriate to adjust the data for population characteristics and placebo response rates.

4.8 The results of the network meta-analyses are presented in table 1. The results for PASI 75 showed that the effectiveness of ustekinumab and adalimumab were similar, and that ustekinumab and adalimumab were more effective than etanercept. The committee heard from the clinical expert that this reflected clinical practice because clinicians are unlikely to offer etanercept as a first biological therapy. The committee was concerned that using adult data could potentially bias the effect estimates, but agreed that this was mitigated by the assessment group having adjusted for population and placebo effects. The committee concluded that, despite the uncertainty associated with the network meta-analyses (see section 4.7), they showed adalimumab, etanercept and ustekinumab to be more clinically effective than placebo and methotrexate. In addition, the committee concluded that ustekinumab and adalimumab had broadly similar effectiveness, and that both were more clinically effective than etanercept.

Table 1. Network meta-analyses results

	%, PASI 75 (95% CrI)	PASI 75 relative risk at 12 weeks, mean (95% CrI)			
		Versus placebo	Versus etanercept	Versus ustekinumab	Versus adalimumab
Etanercept	54 (39 to 69)	5.09 (3.30 to 8.05)	-	-	-
Ustekinumab	82 (71 to 90)	7.91 (4.46 to 14.14)	1.54 (1.28 to 1.92)	-	-
Adalimumab	79 (64 to 90)	7.53 (4.37 to 12.98)	1.47 (1.23 to 1.79)	0.96 (0.85 to 1.05)	-
Methotrexate	49 (31 to 68)	4.55 (3.01 to 6.94)	0.91 (0.66 to 1.15)	0.59 (0.41 to 0.77)	0.62 (0.44 to 0.78)
Placebo	11.5 (5 to 20)	-	-	-	-
Abbreviation: PASI, Psoriasis Area and Severity Index; CrI, credible interval					

Cost effectiveness

Model structure

4.9 The committee considered the assessment group's de novo Markov model. It noted the assessment group had done analyses for 3 different populations based on the position of the technology in the treatment pathway, and the different ages specified in the marketing authorisations for each intervention:

- Population 1 included:
  - children and young people aged 4 years to 17 years
  - people with severe psoriasis eligible for second-line treatment (that is, an alternative to a non-biological systemic treatment)
  - adalimumab and non-biological systemic treatment (methotrexate) as interventions or comparators.
- Population 2 included:
  - children and young people aged 6 years to 11 years

  - people with severe psoriasis eligible for third-line treatment (that is, as an alternative to another biological treatment or best supportive care)
  - adalimumab, etanercept and best supportive care as interventions or comparators.
- Population 3 included:
  - children and young people aged 12 years to 17 years
  - people with severe psoriasis eligible for third-line treatment (that is, as an alternative to another biological treatment or best supportive care)
  - adalimumab, etanercept, ustekinumab and best supportive care as interventions or comparators.

The assessment group's model had 4 health states: 'trial period', 'continued use', 'best supportive care' and 'death'. Patients entered the model in the 'trial period' and had 1 of the 3 biological interventions or a relevant comparator. The modelled PASI response rates were from the assessment group's preferred network meta-analysis. The committee appreciated that young people continue taking biological treatments into adulthood, and may switch treatment, but understood from the assessment group that modelling these treatment sequences was not possible because the relevant data do not exist. The committee was aware that the marketing authorisation for adalimumab included children aged 4 to 6 years and was concerned that population 2 did not include this group of children. It therefore agreed to apply the results from population 2 to children aged between 4 and 6 years, in considering the comparison with best supportive care at third line therapy (after non biological systemic treatments). In addition, the committee agreed that it was more appropriate to consider the cost-effectiveness estimates for populations 2 and 3 together comparing adalimumab and etanercept because they are in the same place in the treatment pathway. The

committee accepted that the assessment group's modelling approach was acceptable for decision-making.

4.10 The committee discussed the length of the time horizon used in the assessment group's model. The assessment group assumed that at the age of 18 years, NICE technology appraisal guidance on etanercept, adalimumab and ustekinumab for biologicals in adults would apply. In the model, the time horizon varied according to population: 14 years for population 1 (aged 4 to 17 years); 12 years for population 2 (aged 6 to 11 years); and 6 years for population 3 (aged 12 to 17 years). The committee heard from one of the companies that a lifetime time horizon was needed to capture the full benefits of costs of treatment because the effects of psoriasis continue into adulthood. The committee was aware that the assessment group did a sensitivity analysis using a common 14-year time horizon. It heard from the assessment group that, in its model, most people had withdrawn from biological treatment after 14 years. It also noted that the time horizon did not have a large effect on the incremental cost-effectiveness ratios (ICERs). The committee concluded that, although a lifelong time horizon would better reflect the treated natural history of disease, given the data available, the assessment group's approach was appropriate.

4.11 The committee considered the stopping rules used by the assessment group in its model, that is, that clinicians should assess and stop treatment in patients whose disease has not responded by week 12 for etanercept, and week 16 for adalimumab and for ustekinumab. It agreed that this was consistent with the guidance in the summary of product characteristics for etanercept and adalimumab, but not for ustekinumab which states that response should be assessed at 28 weeks, rather than 16 weeks. The committee understood that 16 weeks was used in NICE's technology appraisal guidance for ustekinumab for treating moderate to severe psoriasis in adults. The committee agreed that it was desirable to have similar stopping rules for children and adults to avoid unnecessary

changes in care during the transition from children to adult services. In addition, the committee agreed it was appropriate to use PASI 75 to assess response to treatment (see section 4.5). The committee concluded that the assessment group's approach and stopping rules based on PASI 75 were appropriate.

Defining best supportive care

4.12 The committee discussed the challenges of defining best supportive care for psoriasis in children and young people:

- It considered comments from 1 company that most children and young people who get best supportive care have phototherapy. It was aware that the assessment group assumed that 16% of children and young people having best supportive care have phototherapy. The committee heard from the clinical expert that phototherapy was not frequently used because it meant time off school for children and young people as well as time of work for parents or carers. The committee agreed that the assessment group's estimate of 16% was in line with clinical practice and was appropriate.
- It considered comments from 1 company that people whose disease does not respond to treatment with methotrexate would not be given methotrexate as part of best supportive care again. The committee was aware that the assessment group assumed that 61% of patients have methotrexate and 29% have ciclosporin as part of best supportive care. The committee heard that non-biological systematic therapies were valuable and often continued even in the absence of obvious improvement because stopping them may worsen disease. The committee agreed that, although the proportion of people using each therapy as a part of best supportive care was unclear, the assessment group's approach was reasonable.

Withdrawing from treatment

4.13 The committee was aware that, in its model, the assessment group assumed that 20% of people withdrew from biological treatment each year and then used best supportive care instead. The committee understood from the assessment group that there was limited information about the rate at which children and young adults withdraw from biological treatment and so the assessment group applied the same assumption as used in previous NICE technology appraisals for adults. It heard from the clinical expert that adherence to the drugs is greater in children than in adults. The clinical experts also explained that, in practice, if a patients' disease failed to respond to 1 drug, clinicians would offer another biological treatment. If this failed, the clinician would then offer an off-label drug (such as infliximab, which is licensed only in adults) rather than best supportive care. The committee noted that the withdrawal rate did not have a large impact on the ICER and concluded that assuming a 20% withdrawal rate from biologicals to best supportive care was reasonable, but agreed that potentially it could be lower.

Utilities

4.14 The committee discussed the challenges of measuring health-related quality of life in children and young people with psoriasis. The committee appreciated that the assessment group assumed that biological therapies improve quality of life but do not extend life. The committee noted that the trials did not collect data on EuroQol–5 Dimension–Youth (EQ-5D-Y, a generic preference-based measure for quality of life in people aged 8 years to 15 years), and reported only CDLQI and Pediatric Quality of Life Inventory (PedsQL, an approach to measuring health-related quality of life in healthy children and young people, and those with acute and chronic health conditions). In its model, the assessment group mapped PedsQL scores from the CADMUS trial to EQ-5D-Y using a mapping algorithm.

4.15 The committee noted that, when using this mapping algorithm, the quality of life in children and young people at the beginning of the trials was higher than in adults with severe psoriasis (such as in NICE technology appraisal guidance on etanercept, adalimumab and ustekinumab). It also noted that the utility gain associated with an improvement in PASI response in children and young people was lower than in adults. The committee heard that it was implausible that children benefit less than adults, particularly because children experience similar physical symptoms, but some might feel more socially stigmatised than adults. The committee was aware that the assessment group did a sensitivity analysis using utilities from the appraisals of psoriasis in adults and noted that this substantially decreased the ICERs. The committee was concerned that it was not clear how the assessment group had done these sensitivity analyses, for example, whether it had used the baseline utility for adults or for children and young people. On balance, although the committee acknowledged that gain in quality of life associated with an improvement in psoriasis was uncertain, it agreed that it was likely that the increase in quality of life in children and young people would be higher than estimated by the assessment group in its model. The committee would have preferred the assessment group to explore different methodologies to incorporate the adult utility, but without this concluded that it was appropriate to apply the most optimistic adult utility gains to children and young people.

4.16 The committee heard from the clinical and patient experts that carer disutility should be considered when appraising treatments for severe psoriasis in children. The committee heard that children need help administering their treatments (such as applying emollients) and this can be time consuming, especially for best supportive care. The committee appreciated that it was difficult to estimate the disutility associated with psoriasis for parents and carers, and that the assessment group had not incorporated these in its analyses. The committee concluded that it would

take into account the reduced disutility to parents and carers with biological treatments in its decision-making.

Resource use and costs

4.17 The committee considered costs used by the assessment group in its model:

- Number of days in hospital with best supportive care: the committee noted that the assessment group assumed that there were 0 days in hospital with best supportive care after advice from its clinical expert in the absence of evidence. The committee noted comments from the companies that this was too conservative and that the assumption was inconsistent with previous NICE guidance (NICE guideline on psoriasis: 26.60 bed days; and a study on initiation of biological therapy in adults by Fonia et al. [2010]: 6.49 bed days). It heard from the clinical expert that hospitalisation was not common in the paediatric setting and was probably less than 6.49 bed days per year. The committee acknowledged that, because few children and young people with severe psoriasis have best supportive care (with the availability of biologicals) in practice, it was difficult for clinicians to estimate the rate of hospitalisation in these patients. The committee acknowledged that the number of days in hospital was highly uncertain, but also that it had an important effect on the ICER. It agreed that the likely value was between 0 (as assumed by the assessment group) and 6.49 (as in the paper by Fonia et al.).
- The assessment group used cost codes for hospitalisation and for treatment at day centres for adults because it was not clear to them whether these costs for children included the cost of the treatment. The committee heard from the assessment group that using the costs for children could potentially double-count costs of treatment. The committee noted comments from the companies that this underestimated the cost of care for children and young people. The committee agreed that it was likely that the paediatric costs would be

higher than in adults, but acknowledged that the costs of hospitalisation and day centres for children were uncertain.

Cost-effectiveness results and conclusions

4.18 The committee considered the estimates of cost effectiveness calculated by the assessment group. The base-case results were:

- Population 1: the ICER for adalimumab compared with methotrexate was £308,329 per QALY gained.
- Population 2: the ICER for adalimumab compared with etanercept was £174,519 per QALY gained. The ICER for etanercept compared with best supportive care was £71,903 per QALY gained. The ICER for adalimumab compared with best supportive care was £115,825 per QALY gained.
- Population 3: the ICER for adalimumab compared with best supportive care was £110,430 per QALY gained. Etanercept compared with best supportive was extendedly dominated (that is, the ICER for etanercept compared with best supportive care was higher than that of the next, more effective, alternative). The ICER for ustekinumab compared with adalimumab was £201,507 per QALY gained.

4.19 The committee recalled that some of its preferred assumptions differed from the assessment group's base case. These included:

- considering the cost-effectiveness estimates for populations 2 and 3 together for adalimumab and etanercept because they are in the same place in the treatment pathway (see section 4.18).
- using adult utilities for children and young adults (see section 4.16)
- assuming the likely number of days in hospital with best supportive care was between 0 and 6.49 (see section 4.18)
- using higher costs for hospitalisation and for treatment at day centres (see section 4.18)
- including carer utilities (see section 4.18).

The committee agreed that the scenario analysis that most closely matched these assumptions was the assessment group's scenario analysis that combined the effect of using adult EQ-5D data from NICE technology appraisal guidance on etanercept, and which assumed 6.49 days in hospital per year for children and young adults having best supportive care from Fonia et al (2010). However, the committee noted that some of its preferred assumptions were not fully reflected in the scenario analysis and took into account the potential for bias in the ICERs:

- Including carer disutility: the committee agreed that including disutility might reduce the ICERs for more effective treatments.
- Using higher costs for hospitalisation and for treatment at day centres: the committee agreed that these higher costs might reduce the ICERs for more effective treatments.
- Assuming the likely number of days in hospital with best supportive care was lower than 6.49: the committee agreed that a lower number of days in hospital would increase the ICERs for more effective treatments.

Second-line treatment (population 1)

4.20 The ICER for adalimumab compared with methotrexate was £95,527 per QALY gained. Taking into account potential biases (see section 4.19), the committee concluded that the most plausible ICER was unlikely to be at a level at which adalimumab could be considered a cost-effective use of NHS resources for this population.

Third-line treatment (populations 2 and 3)

4.21 The committee considered the cost-effectiveness estimates for populations 2 and 3 together.

- Population 2: the ICER for etanercept compared with best supportive care was £8,897 per QALY gained. The ICER for adalimumab compared with etanercept was £49,274 per QALY gained.

- Population 3:
  - Etanercept was extendedly dominated by adalimumab. The ICER for etanercept compared with best supportive care was £29,177 per QALY gained.
  - The ICER for adalimumab compared with best supportive care was £23,861 per QALY gained. If etanercept was not excluded from the decision problem because of extended dominance, then the ICER for adalimumab compared with etanercept would be approximately £16,000 per QALY gained.
  - The ICER for ustekinumab compared with adalimumab was £61,722 per QALY gained.

4.22 The committee considered the cost effectiveness of etanercept. It took into account the potential biases associated with the ICER (see section 4.19). The committee recognised that etanercept had an ICER of £8,897 per QALY gained in population 2 but was extendedly dominated in population 3. It further noted that, compared with best supportive care the most plausible ICER was likely to be between £8,897 and £29,177 per QALY gained. The committee therefore concluded that on balance, that etanercept could be considered a cost-effective use of NHS resources.

4.23 The committee considered the cost effectiveness of adalimumab. It took into account the potential biases associated with the ICER (see section 4.20). The committee noted that adalimumab was associated with an ICER of £23,861 per QALY gained in population 2, but £49,274 per QALY gained in population 3. It noted that the difference in ICERs was due to their being different comparators in the incremental analyses as adalimumab extendedly dominated etanercept in population 3. The committee noted that in population 3, the ICER for adalimumab compared with etanercept was approximately £16,000 per QALY gained. It concluded that on balance, adalimumab could be considered a cost-effective use of NHS resources.

4.24 The committee considered the cost effectiveness of ustekinumab. It took into account the potential biases associated with the ICER (see section 4.19). The committee concluded that although a range of biological treatment options was desirable (see section 4.2), the most plausible ICER for ustekinumab was £61,722 per QALY gained (compared with adalimumab), and ustekinumab was associated with higher costs that the other technologies. The committee agreed that ustekinumab could not be considered a cost-effective use of NHS resources. The committee tried to identify a subgroup in whom ustekinumab would be cost effective. The committee recognised that, although only a small proportion of people in CADMUS had previous biological therapy (up to 14% of patients in CADMUS), ustekinumab could also be considered in children and young people with severe psoriasis whose disease has not responded to standard systemic therapy and at least 1 biological therapy, for example, adalimumab or etanercept, because this would likely reflect a group of high unmet need. The committee agreed that the ICER for ustekinumab compared with best supportive care was £26,253 per QALY gained and that this would be the most appropriate comparison for people with severe psoriasis whose disease had not responded to at least 1 biological treatment. The committee concluded that ustekinumab could be considered a cost-effective use of NHS resources for this population.

Innovation

4.25 The committee discussed whether adalimumab, etanercept and ustekinumab could be considered as innovative technologies. The committee heard from the clinical expert that these drugs were not novel to the NHS in England. The committee agreed that carer disutilities had not been included in the modelling but should be taken into account (see section 4.17). The committee concluded that there were QALYs that were not fully captured in the modelling.

Equality issues

4.26 The committee was aware of the potential equality issue raised in previous NICE technology appraisals for adults that the PASI can underestimate disease severity in those with darker skin. The committee concluded that, when using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make any adjustments they consider appropriate.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.27 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of any of the technologies in this appraisal.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Adalimumab, etanercept and ustekinumab for treating plaque psoriasis in children and young people**	**Section**
Key conclusion		
Adalimumab is recommended as an option for treating plaque psoriasis in children and young people aged 4 years or older. Etanercept is recommended as an option for treating plaque psoriasis in children and young people aged 6 years or older. Ustekinumab is recommended as an option for treating plaque psoriasis in children and young people aged 12 years or older. The		1.1–1.3; 4.20–4.25

committee concluded that adalimumab, etanercept and ustekinumab could be considered a cost-effective use of NHS resources as a treatment for severe psoriasis in children and young people.		
Current practice		
Clinical need of patients, including the availability of alternative treatments	Children and young people have topical treatments as a first line. If their disease responds inadequately to treatment or if the previous treatment is not tolerated or contraindicated, they can have systemic non-biological therapies (such as methotrexate, ciclosporin and phototherapy) second line. Clinicians then offer children and young people biological therapies or best supportive care third line. If their disease no longer responds to a biological treatment, clinicians offer patients another biological therapy.	4.3
The technologies		

Proposed benefits of the technologies How innovative are the technologies in their potential to make a significant and substantial impact on health-related benefits?	Adalimumab and etanercept inhibit the activity of tumour necrosis factor alpha (TNF-alpha) which is associated with psoriasis. Ustekinumab acts as a cytokine inhibitor by targeting interleukin-12 and interleukin-23, which are associated with psoriasis. The committee concluded that the drugs were not novel to the NHS in England and that there were quality-adjusted life years (QALYs) that were not fully captured in the modelling.	2 4.26
What is the position of the treatments in the pathway of care for the condition?	The committee concluded that adalimumab would be offered as a second- and third -line treatment and etanercept and ustekinumab as a third-line treatment for children and young people with psoriasis.	4.3
Adverse reactions	Adverse reactions are described in the summary of product characteristics for each drug.	2
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The committee considered evidence from the randomised controlled trials: • M04-717 compared adalimumab with methotrexate in children and young people (n=114) aged 4 to 17 years. • 20030211 compared etanercept with placebo in children and young people (n=211) aged 4 to 17 years.	4.4

	• CADMUS compared ustekinumab with placebo in children and young people (n=110) aged 12 to 17 years.	
Relevance to general clinical practice in the NHS	The committee concluded that clinical trial evidence was appropriate for decision-making and generalisable to NHS practice in England.	4.6
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The effectiveness of ustekinumab and adalimumab were similar based on relative effectiveness estimates for PASI 75 (adalimumab compared with ustekinumab 45, relative risk [RR]: 0.96, 95% credible interval [CrI] 0.85 to 1.05). In children and young people, ustekinumab (RR 1.54, 95% CrI 1.28 to 1.92) and adalimumab (RR 1.47, 95% CrI 1.23 to 1.79) are more effective than etanercept.	4.8–4.9
Evidence for cost effectiveness		
Availability and nature of evidence	The committee considered the assessment group's de novo Markov model. It accepted that the model was appropriate for decision-making.	4.10
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee identified the key uncertainties in the assumptions in the economic model, which include: • costs for hospitalisation and for treatment at day centres • not including carers' disutility • number of days in hospital.	4.20

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee would have preferred the assessment group to explore different methodologies to incorporate the adult utility, but without this concluded that it was appropriate to apply the most optimistic adult utility gains to children and young people.	4.16
Are there specific groups of people for whom the technology/ies is/are particularly cost effective?	Ustekinumab could be considered in children and young people with severe psoriasis whose disease has not responded to standard systemic therapy and at least 1 biological therapy, for example, adalimumab or etanercept, because this would likely reflect a group of high unmet need. The committee agreed that the incremental cost-effectiveness ratio (ICER) for ustekinumab compared with best supportive care was £26,253 per QALY gained and that this would be the most appropriate comparison for people with severe psoriasis whose disease had not responded to at least 1 biological treatment.	4.25

What are the key drivers of cost effectiveness?	The committee agreed that: • including carers' disutility might reduce the ICERs for more effective treatments • using higher costs for hospitalisation and for treatment at day centres might reduce the ICERs for more effective treatments • fewer days in hospital would increase the ICERs for more effective treatments.	4.20
Most likely cost-effectiveness estimate (given as an ICER)	The ICER for ustekinumab compared with best supportive care was £26,253 per QALY gained. The most plausible ICER for adalimumab compared with etanercept was likely to be between £16,355 per QALY gained and £49,274 per QALY gained. The most plausible ICER for etanercept compared with best supportive care was likely to be between £8,897 and £29,177 per QALY gained.	4.23–4.25
Additional factors taken into account		
Patient access schemes (PPRS)	The PPRS payment mechanism was not relevant in considering the cost effectiveness of any of the technologies in this appraisal.	4.28

Equalities considerations and social value judgements	The committee was aware that the PASI can underestimate disease severity in those with darker skin. It concluded that, when using the PASI, healthcare professionals should take into account skin colour and how this could affect the PASI score, and make any adjustments they consider appropriate.	4.27

5 Implementation

5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has psoriasis and the doctor responsible for their care thinks that adalimumab, etanercept or ustekinumab is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Proposed date for review of guidance

6.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
March 2017

7 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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Technical Leads

Jasdeep Hayre

Technical Adviser

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