Review proposal of TA433; Apremilast for treating active psoriatic arthritis (rapid review TA372), TA445; Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease modifying anti-rheumatic drugs

TA433 was published in February 2017 and scheduled to be considered for review in 2020.

TA445 was published in May 2017 and scheduled to be considered for review in 2020.

1. Proposal

We propose that TA433 and TA445 are transferred to the 'static' guidance list.

2. Rationale

We did not identify any new clinical evidence that would change the existing recommendations in TA433 and TA445. There are no changes to the marketing authorisations or the prices. There is no new evidence on comparative effectiveness for certolizumab pegol, secukinumab, or apremilast compared with biologics or each other for treating psoriatic arthritis.

3. Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?

There are no changes to the list prices of apremilast, certolizumab pegol and secukinumab since the publication of TA433 and TA445. [redacted].

Biosimilars

There are now biosimilar versions of adalimumab, etanercept and infliximab for treating psoriatic arthritis. TA445, which was published in May 2017, included biosimilars of etanercept and infliximab while TA433, which was published in February 2017, did not. In addition, there have been changes to comparator prices paid by the NHS (specific values are not reported here as these are confidential). The patents for tocilizumab and for certolizumab pegol expire in 2019 and 2021 respectively and biosimilars for these are in development.

Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

There are no existing or proposed changes to the marketing authorisation that would affect the existing guidance.

Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

TA445 included clinical evidence mainly from placebo-controlled trials. There were 2 head-to-head trials, 1 compared secukinumab with ustekinumab and 1 compared infliximab, etanercept and adalimumab. The companies and assessment group presented mixed treatment comparisons to estimate comparative effectiveness. The committee concluded that the relative effectiveness of certolizumab pegol and secukinumab when compared with etanercept, adalimumab, golimumab and infliximab and with each other was uncertain. It recommended certolizumab pegol and secukinumab as alternative treatments to other biologics. New evidence supports this recommendation. We didn't identify additional head-to-head trials for psoriatic arthritis. We identified 2 trials comparing secukinumab with placebo showing that secukinumab is better than placebo. There were no additional trials for certolizumab pegol. We identified long-term data for both certolizumab pegol and secukinumab showing that these treatments are better than placebo for up to 4 and 3 years respectively. These data also showed a favourable safety profile for both treatments. We identified systematic literature reviews and network meta analyses on effectiveness and safety of certolizumab pegol and secukinumab. The results presented in the recent publications broadly support the conclusions in TA445 and are unlikely to change the recommendations.

TA433 included clinical evidence comparing apremilast with placebo. The company used indirect treatment comparison to estimate apremilast's relative effectiveness. The committee concluded that apremilast was less effective than comparator biologics. However, apremilast was less costly than other treatments. It also has a different mechanism of action and can be taken orally. Therefore, the committee recommended apremilast as an alternative treatment. There is no new evidence that would change this recommendation. We didn't identify any trials comparing apremilast with biologics for psoriatic arthritis. There are 2 trials comparing apremilast with placebo showing that apremilast is better than placebo for treating DMARD-naïve and biological-naïve psoriatic arthritis. Additionally, there is long-term data showing that apremilast is better than placebo for up to 5 years. We identified systematic literature reviews and network meta analyses on effectiveness and safety of apremilast. The results presented in the recent publications broadly support the conclusions in TA433 and are unlikely to change the recommendations.

Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

See Appendix C for a list of related NICE guidance.

The search strategies from the original ERG and assessment reports were adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from 23rd June 2014 (for TA433) and 28th April 2016 (for TA445) to 5th November 2019 were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

TA445 takes into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC is described in section 1.4.

Proposal paper sign off

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Appendix A – Information from existing guidance

1. Original remit

TA445 "To appraise the clinical and cost effectiveness of certolizumab pegol and secukinumab within their marketing authorisations for treating active psoriatic arthritis in adults whose disease has not responded adequately to previous disease-modifying anti-rheumatic drug therapy"

TA433 "To appraise the clinical and cost effectiveness of apremilast within its licensed indication for treating active psoriatic arthritis in people for whom disease-modifying anti-rheumatic drugs have been inadequately effective, not tolerated or contraindicated"

2. Current guidance

TA445:

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

- it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2) or
- the person has had a tumour necrosis factor (TNF)-alpha inhibitor but their disease has stopped responding after the first 12 weeks.

Certolizumab pegol is only recommended if the company provides it as agreed in the patient access scheme.

1.2 Secukinumab alone, or in combination with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults only if:

- it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2) or
- the person has had a TNF-alpha inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks or
- TNF-alpha inhibitors are contraindicated but would otherwise be considered (as described in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis).

Secukinumab is only recommended if the company provides it as agreed in the patient access scheme.

1.3 Assess the response to certolizumab pegol and secukinumab after 12 weeks and 16 weeks of treatment respectively. Only continue treatment if there is clear evidence of response, defined as an improvement in at least 2 of the 4 Psoriatic Arthritis Response Criteria (PsARC), 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria. 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 based on skin response (as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, recommendation 1.3).

1.4 When using the PsARC healthcare professionals should take into account any physical, sensory or learning disabilities or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate.

1.5 This guidance is not intended to affect the position of patients whose treatment with certolizumab pegol and secukinumab 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.

TA433:

1.1 Apremilast, alone or in combination with disease-modifying antirheumatic drugs (DMARDs), is recommended as an option for treating active psoriatic arthritis in adults only if:

- they have peripheral arthritis with 3 or more tender joints and 3 or more swollen joints and
- their disease has not responded to adequate trials of at least 2 standard DMARDs, given either alone or in combination and
- the company provides apremilast with the discount agreed in the patient access scheme.

1.2 Stop apremilast at 16 weeks if the psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis response Criteria (PsARC), defined as an improvement in at least 2 of the 4 PsARC criteria (including joint tenderness or swelling score) with no worsening in any criteria. If the disease has a Psoriasis Area

and Severity Index (PASI) 75 response, a dermatologist should decide whether to continue treatment with apremilast after 16 weeks based on skin response.

1.3 When using the PsARC healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to components of the PsARC and make any adjustments they consider appropriate.

1.4 This guidance is not intended to affect the position of patients whose treatment with apremilast 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.

3. Research recommendations from original guidance

Not applicable.

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the Technology Appraisals process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to specify date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Options	Consequence	Selected – 'Yes/No'
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider.	Yes
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

Appendix C – Other relevant information

Relevant Institute work

Published

Abatacept for treating psoriatic arthritis after DMARDs (terminated appraisal) (2019) NICE technology appraisal 568 – *"The company has confirmed that it does not intend to make a submission for this appraisal because the technology will not be launched in the UK (in this indication)".*

Tofacitinib for treating active psoriatic arthritis after inadequate response to DMARDs (2018) NICE technology appraisal 543

Ixekizumab for treating active psoriatic arthritis after inadequate response to DMARDs (2018) NICE technology appraisal guidance 537

Ustekinumab for treating active psoriatic arthritis (2015) NICE technology appraisal guidance 340

Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (2010) NICE technology appraisal guidance 199

Golimumab for the treatment of psoriatic arthritis (2011) NICE technology appraisal guidance 220

Spondyloarthritis in over 16s: diagnosis and management (2017) NICE guideline NG65

Details of changes to the marketing authorisation for the technology

Marketing authorisation and price considered in original appraisal

Apremilast

Apremilast had a marketing authorisation for use alone or in combination with disease-modifying antirheumatic drugs (DMARDs) for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy

List price: £550.00 for a 28-day pack (56 30 mg tablets) (excluding VAT; British National Formulary online, accessed September 2016).

Apremilast is available under the terms of a Patient Access Scheme (PAS) which gives a simple discount to the list price applied at the point of purchase or invoice. The level of the discount is commercial in confidence.

Certolizumab pegol

Certolizumab pegol had a marketing authorisation for use treating active psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug (DMARD) therapy has been inadequate, either:

- in combination with methotrexate or
- as monotherapy, if methotrexate cannot be tolerated or when continued treatment with methotrexate is inappropriate.

The cost of certolizumab pegol was £357.50 per 200 mg prefilled pen or prefilled syringe. Under a PAS the company has agreed that the first 12 weeks of therapy with certolizumab pegol will be free of charge.

Secukinumab

Secukinumab had a marketing authorisation treating active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate, either:

- in combination with methotrexate or
- as monotherapy.

Secukinumab costs £1,218.78 per 2 150 mg prefilled pen or syringe. It is currently recommended under the terms of a Patient Access Scheme (PAS) which gives a simple discount to the list price applied at the point of purchase or invoice. The level of the discount is commercial in confidence.

Proposed marketing authorisation (for this appraisal) and current price

No change to list prices (Drug Tarriff, November 2019; C+D data online, accessed 6th November 2019).

There have been no changes to marketing authorisations relevant to this appraisal.

[redacted]

Registered and unpublished trials

Trial name and registration number	Details
A Phase 4, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of apremilast (CC-10004) in subjects with early, oligoarticular psoriatic arthritis despite initial stable treatment with either NSAIDS and/or = 1 conventional synthetic DMARD FOREMOST; NCT03747939; CC-10004-PSA-013; 2018-002735-26; U1111-1224-0216	n = 330 Currently recruiting Estimated completion date: January 2021 (primary outcome); August 2021 (overall)
Prevention of metacarpophalangeal joints structure damage in patients with psoriatic arthritis using secukinumab NCT03623867; PsA secukinumab XCT study 2018	Randomised, placebo controlled trial in people previously treated with NASIDs or DMARDs n = 40 Not yet recruiting Estimated completion date: June 2022
A randomized, double-blind, placebo-controlled multicenter study of subcutaneous secukinumab to demonstrate efficacy in the treatment of enthesitis at the achilles tendon up to 1 year in adult patients with active psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) NCT02771210; 2016-000972-91; CAIN457F3301	n = 204 Active, not recruiting Estimated completion date: January 2020
A three-part randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of secukinumab treatment in juvenile idiopathic arthritis subtypes of psoriatic and enthesitis-related arthritis NCT03031782; 2016-003761-26; CAIN457F2304	n = 86 Active, not recruiting Estimated completion date: October 2019 (primary outcome); December 2020 (overall)

Trial name and registration number	Details
A randomized, double-blind, placebo controlled, multicenter study of subcutaneous secukinumab, to demonstrate efficacy after twelve weeks of treatment and to assess safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis with or without psoriatic arthritis comorbidity NCT03066609; CAIN457A2318; 2016-000524-25	n = 543 Completed ~ November 2018
A randomized, double-blind, active control, multicenter study to evaluate the efficacy at week 52 of secukinumab monotherapy compared with adalimumab monotherapy in patients with active psoriatic arthritis NCT02745080; CAIN457F2366; 2015-004477-32; EXCEED 1	n = 850 Active, not recruiting Estimated completion date: September 2019 (primary outcome); December 2019 (overall)
MAXIMISE (Managing AXIal Manifestations in PsorIatic Arthritis With SEcukinumab), a randomized, double-blind, placebo-controlled, multicenter, 52 week study to assess the efficacy and safety of secukinumab 150 mg or 300 mg s.c. in participants with active psoriatic arthritis and axial skeleton involvement who have inadequate response to non steroidal anti-inflammatory drugs (NSAIDs) NCT02721966; CAIN457F3302; 2016-000814-31	n = 503 Completed ~June 2019
A 52-week, multicenter study to assess the time course of response to secukinumab on joint inflammation using power doppler ultrasonography in patients with active psoriatic arthritis NCT02662985; CAIN457F2354; 2015-002394-38	Randomised, placebo-controlled trial in people with an inadequate response to non-biologic DMARDs n = 218 Currently recruiting Estimated completion date: November 2020

Trial name and registration number	Details
Dose reduction and discontinuation of biological therapy in patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis: protocol for a 18 months randomised, open label, parallel-group, multi-centre trial 2017-001970-41; 20170508; BIODOPT	Two-arm, dose reduction study on various biological therapies, including certolizumab pegol n = 180 Ongoing Estimated completion date: November 2023