NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Consideration of consultation responses on review proposal

Review of NICE Technology Appraisal; Adalimumab, etanercept, infliximab, rituximab, abatacept (review of TA195), golimumab (part review of TA225) and tocilizumab (part review of TA247) for the treatment of rheumatoid arthritis after failure of disease-modifying anti-rheumatic drugs including a TNF-inhibitor

This guidance was issued in:

TA195 – August 2010

TA225 – June 2011

TA247 – February 2012

The review date for all of these was June 2013.

Background

At the GE meeting of 2 July 2013 it was agreed we would consult on the review plans for this guidance. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

Proposal put to consultees:	The guidance should be transferred to the 'static guidance list' for NICE to proactively monitor future developments. That we consult on this proposal.
Rationale for selecting this proposal	There are a number of contradictory arguments for and against an update of the guidance: • Ongoing or completed relevant trials are either not reporting until end of 2015 or contain uncertain evidence only. • Subcutaneous formulations and biosimilars will be emerging in the next couple of years, some of which

	may affect the cost effectiveness of the current drugs. However, the emergence of biosimilars for rituximab, which is recommended in TA195, is not expected to alter the recommendation for rituximab. • There is currently no NICE guidance for use of certolizumab pegol after failure of a first line biologic. However, certolizumab pegol is currently recommended for 1st line biologics treatment, and the absence of recommendations for 2nd line biologics treatment would not preclude it being used at this stage of the treatment pathway. Carrying out a full MTA to explicitly explore the use of one of many treatment options is not appropriate use of NICE's resources. • There are no significant changes in marketing authorisation indications that would alter the current guidance. A large number of new biologics are awaiting marketing authorisations, but are most appropriately considered in separate appraisals. • NICE is currently reviewing the guidance for first use of a biologic (Rheumatoid arthritis - adalimumab, etanercept, infliximab (TA130), certolizumab pegol (TA186) and golimumab (TA225 part review) - review [ID537]). This is expected to be issued in January 2014. There is potential for the starting and stopping rules applied to treatment decisions to be updated in the guidance. However, starting and stopping rules for 1st line biologics treatment would not affect a 2nd line treatment recommendations. • The NICE clinical guideline for rheumatoid arthritis will be considered for review again after the publication of the MTA (scheduled to review and update TA130, TA186, TA234 and part review of TA225), and may provide for an opportunity for consideration to update TA195, TA225 and TA247 within the guideline. Bearing in mind that several technologies are currently recommended for 2nd line biologics treatment, none of the above issues points towards the need to review the technology appraisals.

GE is asked to consider the original proposal in the light of the comments received from consultees and commentators, together with any responses from the appraisal team. It is asked to agree on the final course of action for the review.

Recommendation post consultation:	The guidance should be transferred to the 'static guidance list' for NICE to proactively monitor future developments.

Respondent	Response to proposal	Details	Comment from Technology Appraisals
AbbVie	Agree (with caveat)	AbbVie considers that it would be appropriate to move the review of TA195 onto the static list at this point in time until the recommendations from the first line biologic RA MTA are finalised (adalimumab, etanercept, infliximab, golimumab, tocilizumab and abatacept) . However, AbbVie considers that it will be important to review the recommendations inTA195 should non-anti TNF drugs continue to be recommended as first line treatment options in NICE guidance. This is important as when TA 195 was developed, the use of tocilizumab and abatacept as first line options was not considered as neither was recommended. This has now led to the situation where tocilizumab or abatacept could be used as first line biologic options then patients could be given rituximab according to the NICE guidance recommendations. This is contradictory to the licensed indication for rituximab which must be given after TNF failure: 'MabThera in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.' (emphasis added in italics). It would be necessary to address this recommendation outside the licence for rituximab if tocilizumab or abatacept	Comments noted. NICE propose to proactively monitor future developments in rheumatoid arthritis guidance. That is, should the review of TA130, TA186, TA224, TA225, TA247 and TA280 result in changes to guidance which impact on the implementation of TA195, TA225 or TA247 then TA195, TA225 and TA247 would be considered for review. NICE could not recommend rituximab outside its licensed indications.

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		are recommended as first line biologic options in the current ongoing MTA.	
Arthritis Care	No Comments	No further comments	Comment noted.
Bristol Myers Squibb	Agree	BMS agrees with the proposal that the review of TAs 195, 225 and 247 should move to the static list	Comment noted.
Department of Health	No Comments	I can confirm that the Department of Health has no comments to make regarding the above appraisal	Comment noted.
Medicines and Healthcare Products Regulatory Agency	No Comments	This is just to say that we don't have any information that impinges on NICE's proposal	Comment noted.
Merck Sharp & Dohme	Agree	MSD acknowledge that the proposed review of “Review of NICE Technology Appraisal; Adalimumab, etanercept, infliximab, rituximab, abatacept (review of TA195), golimumab (part review of TA225) and tocilizumab (part review of TA247) for the treatment of rheumatoid arthritis after failure of disease-modifying anti-rheumatic drugs including a TNF-inhibitor” will not go ahead, and that the existing guidance will be moved to the static list.	Comment noted.

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		MSD understands the rationale for this decision and has no further comments.	
Novartis	No Comments	Novartis does not have any comments on the review described	Comment noted.
Pfizer	Agree	Pfizer is in agreement with NICE's proposal to move the above review to the static list.	Comment noted.
Physiotherapy Pain Assocation and Professional Network of the Chartered Society of Physiotherapy	No Comments	The Physiotherapy Pain Association (PPA), Professional Network of the Chartered Society of Physiotherapy (CSP) have no comment to make on this.	Comment noted.
Primary Care Rheumatology Society	No Comments	The Primary Care Rheumatology Society have no comments to make on this Appraisal.	Comment noted.
Royal College of Nursing	Disagree	The Royal College of Nursing welcomes the opportunity to comment on proposals regarding the review of the above multiple health technology appraisal guidance. The RCN's comments on the proposals are set out below:	Comments noted, please find the response below in the corresponding bullets: • The effectiveness of rituximab in

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		• TA195 – The RCN considers that this guidance should not be put on the static list and should be reviewed again. The effectiveness of Rituximab in sero positive RA patients is much greater than in patients who are sero negative, and so in the best interests of sero negative patients (re: clinical outcome and cost effectiveness), these patients should have the option of trying a different second line biologic therapy (as an alternative to Rituximab), following failure of a first line anti TNF therapy. The guidance will therefore, benefit from a review before being placed on a static list. • TA195 - (Aug 2010) - Since this was developed a rapid review of technology appraisal has been undertaken (April 2013) (TA280) in which Abatacept has been approved for use as a first line biologic treatment. Although Abatacept has first line NICE approval, some colleagues have recently experienced some difficulties regarding the use of subcutaneous (s/c) Abatacept versus IV Abatacept, as s/c Abatacept use has not been specifically stated in TA280. Hence the barriers to prescribing s/c Abatacept are limiting patient choice and convenience. However, we anticipate that s/c Abatacept will be covered in the ongoing Multiple Technology Appraisal (MTA) for the first-line treatment of rheumatoid arthritis [ID537] if not then this will benefit from a review.	sero positive and sero negative patients was considered in the development of TA195. NICE understands that since development of TA195, no further evidence to add clarity to this issue has been developed. During development of TA195, *"the Committee heard from the clinical specialists that the presence of auto-antibodies is not a consistent measure in that the same person may have a positive test for auto-antibodies in one instance and a negative test in another. The Committee also heard from clinical specialists that draft guidelines from the British Society for Rheumatology advise that people who test seropositive for either rheumatoid factor or anti-CCP may be more likely to respond than people who test seronegative for the two antibodies, and that this should be taken into account when considering rituximab. On balance, the committee was not persuaded that there was currently sufficient*

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		• TA 247 (2012) - We have been waiting for NICE to review Tocilizumab mono therapy (not in combination with Methotrexate). This is of particular relevance and importance to those patients who are unable to tolerate Methotrexate (or when Methotrexate is contraindicated) and who, under existing NICE guidance are only able to take mono therapy TNF inhibitors. If these patients fail to respond to a first line TNF inhibitor, then current NICE guidance recommends another mono therapy TNF inhibitor. To that end, there is new evidence from recent trials about the superiority of Tocilizumab mono therapy over Adalimumab mono therapy. The ADACTA study (2013), shows I/V Tocilizumab (mono therapy) to have superior efficacy over Adalimumab (mono therapy) in reducing disease activity in patients with severe rheumatoid arthritis. Tocilizumab mono therapy should be included as a second line biologic treatment option, otherwise mono therapy patients are being disadvantaged in effective treatment choices. We consider that the recent evidence on Tocilizumab as mono therapy needs to be considered before placing TA247on the static list. • TA225 - We are not aware of any new evidence on Golimumab to change its static status.	*evidence to conclude that rituximab treatment was inappropriate for people who test seronegative. Therefore, the Committee agreed not to make differential recommendations for a subgroup based on auto-antibody status."* • The use of subcutaneous abatacept as a first line biologic treatment is being considered in the currently on-going MTA of the first line biologic treatments (review of TA130, TA186, TA224, TA225, TA247 and TA280) • The ADACTA clinical trial excluded patients previously treated with DMARDS and therefore would not provide evidence to support tocilizumab monotherapy at the point in the treatment pathway to which this review relates. NICE understands that no further evidence is available to show the effectiveness of tocilizumab monotherapy for patients after

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			failure of a TNF inhibitor. The use of tocilizumab monotherapy (including the data from ADACTA) is being considered in the ongoing MTA of first line biologic treatments. • Comment noted.
Royal College of Pathologists	No Comments	I am just writing to inform you that The Royal College of Pathologists does not have any comments to make on this review.	Comment noted.
Roche Products	Agree	The proposal to delay the review of Rheumatoid Arthritis guidance that relates to the TNF-IR indication seems appropriate. We are not aware of any new evidence that would have a material effect on the current guidance, and are therefore supportive of reviewing the TNF-IR indication following the completion of the DMARD-IR MTA [ID537]. Our one concern is that NICE are yet to publish guidance on the use of tocilizumab in those patients that cannot or will not receive methotrexate and have had an inadequate response to a TNF (2nd line). While the current MTA [ID537] will review tocilizumab monotherapy in 1st line, to our knowledge a positive recommendation would be unfortunately limited by the scope of the appraisal, and therefore not include 2nd line use on tocilizumab.	Comment noted. NICE understands that no further evidence is available to show the effectiveness of tocilizumab monotherapy for patients after failure of a TNF inhibitor.

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		We would welcome a pragmatic approach to ensuring the delay does not unfairly leave patients who cannot or will not take methotrexate without an effective alternative treatment following an inadequate response to a TNF.	
UCB Pharma	Disagree	UCB welcomes the opportunity to comment on the NICE proposal paper regarding the review of the technology appraisal TA195, TA225 and TA247 (part review). Following a thorough review of the proposal paper this document summarizes UCB's comments. UCB welcomes NICE consideration to review and update the recommendations for treating adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumor necrosis factor (TNF) inhibitor. **Key point summary** • NICE's guidance on treatments for rheumatoid arthritis (RA) after failure of a TNF inhibitor (i.e., second line treatment – TA195) recommends that TNF inhibitors be use when rituximab is contraindicated or where there is an adverse event. Certolizumab pegol (CIMZIA®) was not included within the original remit TA195 due to marketing authorization timings. • NICE has considered reviewing this guidance, however has considered moving the guidance to the	Comments noted. NICE recognise that Certolizumab pegol was not included within the original MTA due to the timings of marketing authorisations. However, carrying out a full MTA to explicitly explore the use of one of many treatment options is not an appropriate use of NICE's resources, and the absence of guidance at this particular stage in the treatment pathway does not preclude the use of certolizumab pegol. NICE recognise the complexity of the current guidance and propose to proactively monitor future developments in rheumatoid arthritis guidance. That is, should the review of TA130, TA186, TA224, TA225,

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		"static list" for several reasons explained in the Guidance Executive paper. • Certolizumab pegol (CIMZIA®) has been approved by NICE as a first line biologic treatment for RA. Certolizumab pegol is available with a patient access scheme (PAS), that provides the first 12 weeks (10 vials) for free. (TA186, February 2010) • Since the initial review of TA195, new evidence on the efficacy and safety of certolizumab pegol treatment in a broad range of clinically relevant patient groups that are reflective of the types of patients seen in real-life, including TNF-IR has been published. The REALISTIC study assessed the certolizumab pegol use in DMARD-IR and TNF-IR groups and demonstrated the CZP efficacy in both patient groups. • A significant decrease of CZP use in TNF-IR was noticed following the publication of the TA195 guidance, despite the fact that the guidance does not recommend against the use of CZP in TNF-IR due to the non inclusion within its remit. The lack of supportive guidance is preventing uniform use of biologics in TNF-IR patients and prevents clinicians from considering certolizumab pegol as a treatment option in this patient population. , • The ongoing NICE review of biologic treatment in moderate to severe RA patients which are naïve or have failed conventional DMARDs, could potentially	TA247 and TA280 result in changes to guidance which impact the implementation of TA195, TA225 or TA247 then TA195, TA225 and TA247 would be considered for review. NICE recognise that the studies on page 16 and 17 of the Guidance Executive paper are listed by sponsor, with the exception of NCT01500278. The Guidance Executive paper cannot be updated at this stage.

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		extend the use of biologics. In order to provide additional treatment options for RA patients and improve their quality of care, it is therefore even more necessary to review the use of biologics as 2nd line treatment options. **Conclusion** Based on the arguments summarized above and outlines in this document, UCB suggests that NICE reconsiders the recommendation of the guidance executive to place the review of TA195 onto the static list. The review of the guidance will allow consideration and use of certolizumab pegol in this 2nd line position, and additionally ensure effective sequencing pathway that will improve the quality and homogeneity of care of RA patients, in England and Wales. **1.1 Context** NICE is considering the review of existing guidance on using adalimumab, etanercept, infliximab, rituximab, golimumab tocilizumab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor in the NHS in England and Wales (as represented in TA195, TA225 and TA247). It is the view of the Guidance Executive that this review should be moved to the static guidance list with ongoing monitoring, but no proposal to immediately review this guidance. According to the Guidance Executive paper, this decision is driven by four key factors: 1) Ongoing trial and the evolving evidence base	

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		2) The clarity of existing guidance on biologics use in this area 3) The ongoing review of TA130, TA186, TA225 and TA247 4) The emergence of biosimilar therapies UCB is pleased to notice that NICE acknowledges the fact that certolizumab pegol was not included within the original remit TA195 due to marketing authorization timings and that it could be appropriate to include certolizumab pegol in this review of this guidance, alongside the other TNF inhibitors (Guidance Executive paper, page 8). Based on the arguments outlined below, UCB requests that NICE reconsiders this decision to review the existing guidance as there is additional new evidence that has not been considered and that a level of uncertainty exists in terms of cost effective prescribing (and sequencing) which would be improved by a review in this area. **1.2 Ongoing trials and the evolving evidence base** Since the NICE 195 review in 2010, new evidence has been published on the efficacy and safety of certolizumab pegol in TNF inadequate response patients (TNF-IR), demonstrating similar treatment benefits in patients that are cDMARD-IR and TNF-IR. This evidence was not available to the Committee at the time of the previous review and UCB believes it will further help in demonstrating the value of TNF-α inhibitors use in RA patients who have been previously treated with TNF-α inhibitors. Certolizumab pegol has demonstrated efficacy in a broad	

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		range of clinically relevant patient groups that are reflective of the types of patients seen in real-life, including TNF-IR. Certolizumab pegol efficacy and safety in TNF-IR were similar to those demonstrated in TNF-naïve patients. Weinblatt et al (Rheumatology 2012; 51:2204-2214) recently reported the outcomes of the randomised controlled REALISTIC phase IIIb study (NCT00717236) designed with the objective of investigating the efficacy and safety of certolizumab pegol (CZP) in a broad population of patients with active rheumatoid arthritis (RA). Eligible patients had adult onset, active RA (defined by at least 5 tender and at least 4 swollen joints) and patients were excluded if they received treatment with either more than 2 TNF inhibitors, rituximab or abatacept (tocilizumab had not received marketing authorisation at the time of this study). 1063 patients were randomised 4:1 to receive CZP (400mg weeks 0,2 and 4 followed by 200mg every other week (Q2W)) or placebo in addition to their existing RA treatment, cDMARDs. The primary efficacy endpoint in the REALISTIC study was the proportion of patients achieving a 20% improvement in the ACR criteria for the assessment of RA at week 12, secondary endpoints included reduction in disease activity measured by DAS28 at week 12, and other clinical and health outcome measures The results of this study showed that after 12 weeks, treatment with CZP both as monotherapy or with concomitant DMARDs was associated with rapid and consistent clinical responses reducing disease activity and improving physical function in patients with or	

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		without previous TNF inhibitor use, regardless of their baseline MTX use or disease duration. These findings suggest that CZP is effective in a broad, clinically relevant population of patients with active RA. In TNF-IR patients, certolizumab pegol has demonstrated similar efficacy in pts irrespective of the reason of prior TNF discontinuation (efficacy or due to non-efficacy) and number of prior TNFs. Of the total population 37.6% (n=400) of the patient in the REALISTIC study had previous TNF inhibitor use and analysis of this population was a pre-specified baseline stratification factor. The results of this pre-specified baseline stratification analysis of patients with active RA and previous TNF inhibitor use demonstrated that 47.2% of the population treated with CZP achieved a 20% improvement in the ACR criteria for the assessment of RA at week 12, significantly more than those in the placebo group (27.5%; p<0.001). ACR20 response rates were similar among CZP patients, irrespective of whether they discontinued TNF inhibitors for reasons of efficacy (49.7%) or non-efficacy (44.3%), and similar proportions of CZP patients previously receiving one or two TNF inhibitors achieved ACR20 response rates at week 12 regardless of whether they received adalimumab (45.0%), etanercept (52.4%) or infliximab (46.4%). Furthermore in post hoc analysis patients with active RA and previous TNF inhibitor use treated with CZP achieved a 1.79 mean reduction in DAS28 from baseline, representing a 27.9% improvement at week 12 compared to a 1.13 (17.6%)	

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		improvement from baseline in the placebo group. The efficacy of CZP in patients previously exposed to TNF inhibitor was comparable to the one in patients with no previous TNF inhibitor use in the REALISTIC study (53% ACR20 responders and 1.91 improvement in mean change from baseline in DAS28). Regarding the tolerability profile of CZP in REALISTIC was found to be similar to that of previous CZP trials and no new safety signals for CZP were indicated by this study. The data from the REALISTIC study demonstrated that treatment with CZP in patients with active RA and previous TNF inhibitor use can offer clinical benefits and significantly improve disease activity, similar to that achieved by patients with no previous TNF inhibitor use. Although there are significant differences in the trial design and patient populations, and caution should be used when comparing these studies the outcomes of the REALISTIC study compare favourably with those from GO-AFTER. The availability of randomised controlled trials (RCT) of TNF inhibitors in active RA patients with previous TNF inhibitor exposure is limited, with the only other RCT we are aware of with a similar patient population to that of the pre-specified baseline stratification analysis of REALISTIC described above is the GO-AFTER study of golimumab (GLM) in patients with active rheumatoid arthritis after treatment with TNF inhibitors (Smolen et al; Lancet 2009; 374:210-21). In this study patients had adult onset, active RA (defined by at least 4 tender and at least 4 swollen joints) and must have been treated with at least one dose of a TNF inhibitor. 461 patients	

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		were randomised 1:1:1 to placebo, GLM 50mg Q4W or GLM 100mg Q4W in addition to existing treatment to assess a primary endpoint of a 20% improvement in the ACR criteria for the assessment of RA at week 14 and secondary endpoints including improvement in DAS28. 35% of the population treated with GLM 50mg Q4W and 38% treated with GLM 100mg Q4W achieved a 20% improvement in the ACR criteria for the assessment of RA at week 12, significantly more than those in the placebo group (18%; p=0.0006 and p=0.0001 respectively). In addition the patients receiving GLM 50mg Q4W had a median improvement from baseline in DAS28 of 15.7% at week 14 and those receiving GLM 100mg Q4W had an improvement of 21.5% at the same timepoint. Additionally registry data from the BSRBR demonstrates that there is a significant improvement in HAQ in patients who switch to a second TNF inhibitor for treatment of active RA (Hyrich et al, Rheumatology 2008; 41:100-1005). There is clear evidence from both RCT and registry sources to demonstrate that TNF inhibition is a choice for patients with active RA who fail on their first TNF inhibitor, and that CZP is an effective option in these patients. Given the new level of evidence of the efficacy and safety of certolizumab pegol in TNF-inhibitor inadequate responders from a large RCT of more than 1000 patients, out of which 400 are TNF-IRs, UCB feels that NICE should consider this evidence further in the review of the guidance and before making a decision on moving the guidance to the static list.	

Respondent	Response to proposal	Details	Comment from Technology Appraisals
		1.3 The clarity of existing guidance on biologics use As indicated on page 8 of the Guidance Executive paper, certolizumab pegol was not included within the original remit TA195 due to marketing authorization timings and that it could be appropriate to include certolizumab pegol in this review of this guidance, alongside the other TNF inhibitors. As noted on page 2 of the Guidance Executive paper: "There is currently no NICE guidance for the use of certolizumab pegol after the failure of a first line biologic". However certolizumab pegol is recommended for 1st line use and the absence of recommendations for 2nd line biologics treatment would not preclude it being used at this stage of the treatment pathway" At the time of the release of the FAD for TA195 there was a significant use (44%) of certolizumab pegol in patients who had been previously treated with a TNF-inhibitor. When the TA195 was issued in August 2010 a significant reduction was noticed in the level of new patients treated with a previous TNF-inhibitor. Furthermore data from June 2013 indicated that only 13% of patients placed onto certolizumab were TNF-IR. This evidence demonstrates that there is a significant level of uncertainty about the approval for the use of certolizumab pegol in TNF-IR patients which contradicts the statement in the Guidance Executive paper. In addition, there is also significant uncertainty on the sequencing of first line biologic treatment. As the Guidance Paper notes on page 8 under other considerations: "The current guidance does not allow for the range of	

Respondent	Response to proposal	Details	Comment from Technology Appraisals
		scenarios that may occur in clinical practice, when following NICE guidance". Since the publication of TA195 the environment has become significantly more complex, making the need for this review even more necessary, in order to provide additional treatment options for RA patients and improve their quality of care. **1.4 The ongoing review of TA130, TA186, TA225 and TA247** Certolizumab pegol was recommended for use in the NHS by NICE in February 2010 (TA 186) for the treatment of rheumatoid arthritis after inadequate response to conventional DMARDs (i.e., first-line biologic DMARD use). As an antibody against TNF-α, certolizumab pegol is in the same therapeutic class as three of the other drugs considered in this appraisal, namely adalimumab (ADA), infliximab (IFX) and etanercept (ETA). A novel patient access scheme (PAS) for certolizumab pegol was approved by the Department of health in September 2010 and is currently in place. Under this scheme the first 12 weeks (10 vials) are provided by UCB free of charge to the NHS. NICE currently conducts a review of the use of biologics in rheumatoid arthritis (ID537) which is expected to consider the expansion of use in moderate patients who have a DAS score below 5.1 (review of TA130, TA186, TA225 (part review) and TA247) as well as patient which have not been treated with conventional DMARDs. The outcome of this review could lead to more patients being treated with biologics, especially at an earlier stage of the disease. It will be thus necessary to revise	

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		the positioning of the sequencing of biologic therapies to ensure consistency with the current guidance. **1.5 The emergence of bio-similar therapies** In June 2013 the European Medicines Agency approved the use of two infliximab biosiliar therapies, Inflectra (developed by Hospira) and Remsima (developed by Celltrion). The Guidance Executive paper recognises that the arrival of biosimilar treatments into the TNF inhibitor marketplace has the potential to disrupt the current pricing and use structure.: “The emergence of infliximab biosimilars into the market towards the end of 2014 could alter the cost effectiveness of infliximab. However as infliximab is an intravenous agent, the costs will be driven by administration costs as well as drug price”. The assumption that the costs will be driven by the administration structure does not take into account the recent development of Homecare delivery for infusion treatments and the willingness of manufacturers to either bear this cost directly or implement a PAS to absorb these extra costs (TA247, Tocilizumab for the treatment of RA). Further delays in the review of the guidance could potentially impact any possible savings presented by biosimilars of TNF-inhibitors that will not be available to the NHS as these drugs will be considered beyond use as they have not been “approved” by NICE. **1.6 Further comments** The Guidance Executive paper provides a list of supporting information, including ongoing studies (page 16). All	

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		registered and unpublished trials are listed by the active biologic treatment, ordered by sponsor. One of the identified ongoing studies (page 17) is the UCB sponsored study, NCT01500278 (A Multicenter, Single-blind, Randomized Parallel-group Study to Assess the Short- and Long-term Efficacy of Certolizumab Pegol Plus Methotrexate Compared to Adalimumab Plus Methotrexate in Subjects With Moderate to Severe Rheumatoid Arthritis Responding Inadequately to Methotrexate). The way this study is listed does not accurately indicate that this is an UCB sponsored study. UCB requests the correction of the subheading and the replacement of the current subheading text “Adalimumab (as a comparator):” with “Certolizumab pegol”, to ensure consistency with the way all other studies are presented.	
National Rheumatoid Arthritis Society		One area for which there is further evidence is ritux mainly working in seropositive RA, and this might impact on second line therapy guidance. Also there are biologic pathways which are now being agreed by CCGs (and formerly PCTs) which are outside NICE but which have been jointly agreed between the commissioners and the local clinicians which give rheumatologists more flexibility to exercise clinical judgement which is in the best interests of the individual patient and gives patients more choice about mode of administration which can impact hugely on lifestyle and work. I attach an example which has been anonymised.	Comments noted. The effectiveness of rituximab in sero positive and sero negative patients was considered in the development of TA195. NICE understands that since development of TA195, no further evidence has been developed that adds clarity to this issue for this patient population (that is, after failure of a TNF inhibitor). During development of TA195, *“the Committee heard from the clinical specialists that the*

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		My overwhelming concern is that we enable clinicians to exercise clinical judgement which includes taking into account patient preference in terms of mode of administration to fit into lifestyle, rather than arbitrarily forcing them into taking a decision which is not in the best interests of each individual patient. There are biomarkers and safety/side effect concerns which are known now, although much important research continues in this area, and we must heed that science because not to, would surely be to the detriment of patient quality of care.	*presence of auto-antibodies is not a consistent measure in that the same person may have a positive test for auto-antibodies in one instance and a negative test in another. The Committee also heard from clinical specialists that draft guidelines from the British Society for Rheumatology advise that people who test seropositive for either rheumatoid factor or anti-CCP may be more likely to respond than people who test seronegative for the two antibodies, and that this should be taken into account when considering rituximab. On balance, the committee was not persuaded that there was currently sufficient evidence to conclude that rituximab treatment was inappropriate for people who test seronegative. Therefore, the Committee agreed not to make differential recommendations for a subgroup based on auto-antibody status."* NICE acknowledge the clinical guidelines provided. NICE recognise that certolizumab pegol was not included within the original MTA due

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			to the timings of marketing authorisations. However, carrying out a full MTA to explicitly explore the use of one of many treatment options is not an appropriate use of NICE's resources, and the absence of guidance at this particular stage in the treatment pathway does not preclude the use of certolizumab pegol. NICE understands that no further evidence is available to show the effectiveness of tocilizumab monotherapy for patients after failure of a TNF inhibitor.

No response received from:

Patient/carer groups	General
• Action on Pain • Afiya Trust • Arthritic Association • Arthritis and Musculoskeletal Alliance • Back Care • Black Health Agency • Disability Rights UK • Equalities National Council	• Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Commissioning Support Appraisals Service • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland

- Independent Age
- Leonard Cheshire Disability
- Muslim Council of Britain
- Muslim Health Network
- Pain Concern
- Pain Relief Foundation
- Pain UK
- South Asian Health Foundation
- Specialised Healthcare Alliance

Professional groups

- Association of Surgeons of Great Britain and Ireland
- British Association for Services to the Elderly
- British Geriatrics Society
- British Health Professionals in Rheumatology
- British Institute of Musculoskeletal Medicine
- British Institute of Radiology
- British Orthopaedic Association
- British Pain Society
- British Society for Rheumatology
- British Society of Rehabilitation Medicine
- Rheumatoid Arthritis Surgical Society
- Royal College of General Practitioners
- Royal College of Physicians
- Royal College of Radiologists
- Royal College of Surgeons
- Royal Pharmaceutical Society
- Royal Society of Medicine
- United Kingdom Clinical Pharmacy Association

- National Association of Primary Care
- National Pharmacy Association
- NHS Alliance
- NHS Commercial Medicines Unit
- NHS Confederation
- Scottish Medicines Consortium

Comparator manufacturers

- Actavis UK (azathioprine, leflunomide)
- Arrow Generics (azathioprine)
- Aspen (azathioprine)
- Bristol Laboratories (hydroxychloroquine)
- Creo Pharma (hydroxychloroquine)
- Crescent Pharma (sulfasalazine)
- Dexcel Pharma (ciclosporin)
- Hameln Pharmaceutical (methotrexate)
- Hospira UK (methotrexate)
- Medac UK (leflunomide, methotrexate)
- Mercury Pharma Group (methotrexate)
- Mylan (azathioprine, ciclosporin, sulfasalazine, penicillamine)
- Orion Pharma (UK) (methotrexate)
- Rosemont Pharmaceuticals (sulfasalazine)
- Sandoz (azathioprine, leflunomide, methotrexate)
- Sanofi (hydroxychloroquine, leflunomide, sodium aurothiomalate)
- Teva UK (azathioprine, ciclosporin, hydroxychloroquine,leflunomide, methotrexate, penicillamine, sulfasalazine)
- Wockhardt (methotrexate)
- Zentiva UK (leflunomide)

Others • NHS England • NHS Stafford and Surrounds CCG • NHS Warrington CCG • Welsh Government	Relevant research groups • Arthritis Research UK • Bone Research Society • Chronic Pain Policy Coalition • Cochrane Musculoskeletal Group • Health Research Authority • MRC Clinical Trials Unit • National Institute for Health Research • Research Institute for the Care of Older People • The Work Foundation Assessment Group • National Institute for Health Research Health Technology Assessment Programme Associated Public Health Groups • Public Health England • Public Health Wales NHS Trust

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