National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor [ID824]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	UCB Pharma	• 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 used when rituximab is contraindicated or where there is an adverse event. • Certolizumab pegol (CIMZIA®, CZP) was not included within the original remit of TA195 due to marketing authorization timings. • Since the initial review of TA195, evidence on the efficacy and safety of certolizumab pegol treatment in a broad range of clinically relevant patient groups reflective of the types of patients seen in real-life, including TNF- inadequate responders (IR) has been published. The REALISTIC study (NCT00717236) assessed the efficacy and safety of certolizumab pegol in a broad population of patients with active RA, including subjects naïve and previously exposed to anti-TNF. Results from this study indicated that certolizumab pegol was associated with rapid and consistent clinical responses and improved physical function in a diverse group of RA patients, irrespective of concomitant or previous therapy. • The ongoing NICE review of biologic treatment in moderate to severe RA patients which are naïve or have failed conventional	Comments noted. A single technology appraisal of certolizumab pegol has been scheduled into the NICE work programme.

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		DMARDs may introduce starting and stopping rules for 1st line biologics treatment however would not address the gap in understanding of CZP as an option in patients who have failed a TNF. 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. • The review of the use of certolizumab pegol in subjects previously exposed to biologics will improve the quality and homogeneity of care of RA patients, in England and Wales. • As there is new evidence that has not been considered in the previous TA195 guidance and a level of uncertainty may exist in terms of cost effective prescribing, this could be improved by a review of certolizumab pegol in this population.	
	AbbVie	AbbVie considers it would be appropriate to consider all TNF inhibitors in an MTA for use after failure of a TNF inhibitor rather than conducting an STA only for certolizumab, if it is agreed that there is value in NICE appraising switching TNF inhibitors in RA in case of treatment failure .	Comment noted. In September 2013, the recommendations from TA195, TA225 and TA247 relating to the treatment of rheumatoid arthritis after the failure of a DMARD (including a TNF-inhibitor) were reviewed. Following a period of consultation, the recommendations have been moved to the static list and will be proactively monitored for future developments. As part of that review, the Institute noted that there is currently no NICE guidance for use of certolizumab pegol. It considered carrying out a

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			full MTA to explicitly explore the use of one of many treatment options, but considered that it would not be an appropriate use of NICE's resources, given that the evidence base for treatments with existing guidance remains unchanged. Having consulted on this topic and taking into account the review decision for TA195, TA225 and TA247, the Institute decided that a single technology appraisal of certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor was appropriate.
	Bristol-Myers Squibb (BMS)	BMS question the appropriateness of undertaking this STA at this time, given the outcome of the ongoing first-line biologics in RA MTA "ID537: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis (review of TA guidance 130, 186, 224, 234 and part review of TA guidance 225 and 247)" is yet to be completed and the outcome of ID537 could influence the decision problem for this proposed appraisal. Furthermore the outcome of this appraisal may influence the downstream treatment pathway in ID537. It was implied at the first AC meeting in this MTA that a further MTA may follow to investigate cost-effectiveness of biologics after first line.	Comment noted. In September 2013, the recommendations from TA195, TA225 and TA247 relating to the treatment of rheumatoid arthritis after the failure of a DMARD (including a TNF-inhibitor) were reviewed. Following a period of consultation, the recommendations have been moved to the static list and will be proactively monitored for future developments. As part of that review, the Institute noted that there is currently no NICE guidance for use of certolizumab

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			pegol. It considered carrying out a full MTA to explicitly explore the use of one of many treatment options, but considered that it would not be an appropriate use of NICE's resources, given that the evidence base for treatments with existing guidance remains unchanged. Having consulted on this topic and taking into account the review decision for TA195, TA225 and TA247, the Institute decided that a single technology appraisal of certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor was appropriate.
	National Rheumatoid Arthritis Society	As Cimzia is already being used post TNF failure in patients (I am an example, but sadly Cimzia didn't work for me), where: • If rituximab is contraindicated or withdrawn, adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are now recommended as treatment options. • If rituximab therapy cannot be given because methotrexate is contraindicated or withdrawn because of an adverse event, adalimumab and etanercept, each as monotherapy, are now recommended as treatment options. Is it actually necessary to go to the expense of an STA? TNFs are used within NICE guidance post one TNF failure already, where RTX inappropriate, so couldn't this just be a further option available? All the other TNFs are considered options in such	Comment noted. In September 2013, the recommendations from TA195, TA225 and TA247 relating to the treatment of rheumatoid arthritis after the failure of a DMARD (including a TNF-inhibitor) were reviewed. Following a period of consultation, the recommendations have been moved to the static list and will be proactively monitored for future developments. As part of that review, the Institute noted that there is currently no NICE

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		circumstances or is it that the manufacturers are seeking to have Cimzia offered as an equal to Rituximab in the pathway post TNF failure? If that is the case, given their licences permit, wouldn't all the TNFs have to be given similar consideration? I may be wrong on the above but just trying to save everyone time and money!	guidance for use of certolizumab pegol. It considered carrying out a full MTA to explicitly explore the use of one of many treatment options, but considered that it would not be an appropriate use of NICE's resources, given that the evidence base for treatments with existing guidance remains unchanged. Having consulted on this topic and taking into account the review decision for TA195, TA225 and TA247, the Institute decided that a single technology appraisal of certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor was appropriate.
	Merck Sharp and Dohme,	No comments.	No action required.
	Pfizer	No comments.	No action required.
	Roche Products	No comments.	No action required.
Wording	UCB Pharma	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?* Yes.	No action required.
	National Rheumatoid Arthritis Society	Yes.	No action required.

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	AbbVie	The decision to prescribe a second TNF inhibitor after failure of the first may be due to lack of efficacy, loss of efficacy or adverse events. If the decision is taken to proceed with an appraisal to consider switching to another TNF inhibitor it would be appropriate for the appraisal to assess switching for adverse event reasons as well as inadequate response.	Comment noted. Following consultation it was decided that this appraisal of certolizumab pegol would consider the same type of failure as considered in TA195 (that is lack of efficacy and loss of efficacy). For clarity, the remit has been amended to state 'after inadequate response to a TNF inhibitor' rather than 'after failure of a TNF inhibitor'.
	Bristol-Myers Squibb	No comments.	No action required.
	Merck Sharp and Dohme	No comments.	No action required.
	Pfizer	No comments.	No action required.
	Roche Products	No comments.	No action required.
Timing Issues	UCB Pharma	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 2015. There is potential for the starting and stopping rules applied to treatment decisions to be updated in the guidance. However there is still a need for guidance on other biologic options as 2nd line.	Comments noted. A single technology appraisal of certolizumab pegol has been scheduled into the NICE work programme.
	Bristol-Myers Squibb	As stated in the appropriateness section, the timing of this STA, which should be informed by the ongoing MTA ID537, seems premature. In addition, given ID537 is ongoing, it seems possible that the advisory group model could be utilised to inform	Comment noted. Having consulted on this topic and taking into account the review decision for TA195, TA225 and TA247, the Institute decided that a single

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		subsequent treatment modelling	technology appraisal of certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor was appropriate.
	National Rheumatoid Arthritis Society	See comments on appropriateness, above.	Comments noted. See response above.
	AbbVie	No comments.	No action required.
	Merck Sharp and Dohme	No comments.	No action required.
	Pfizer	No comments.	No action required.
	Roche Products	No comments.	No action required.
Additional comments on the draft remit		None.	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action
Background information	UCB Pharma	• As per TA195, we feel the scope should reflect the broader and severe impact that RA and its co-morbidities bring on the quality of life of patients with RA; fatigue and depression are common among people with RA. Furthermore, it is estimated that 40% of people will stop	Comments noted. The aim of the background section is to provide a brief introduction to the disease. The draft scope stated that rheumatoid arthritis has a severe impact on quality of life and approximately one-third of people stop

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		working within 5 years of diagnosis. Rheumatoid arthritis also impacts on mortality, with the risk of cardiovascular disease approximately doubled when compared to the rest of the population. • The scope also does not mention how patients are currently managed which is important when understanding the complexities involved in managing RA patients. It is important to note that generally patients are currently managed by specialist teams in an out-patient setting and then move on to shared care between the primary and secondary care sectors once control is achieved.	work within 2 years. The background section is not intended to explain the settings in which healthcare is provided, although it does refer to published NICE guidance which provides more detail about this. No action required.
	AbbVie	No comments.	No action required.
	Bristol-Myers Squibb	No comments.	No action required.
	Merck Sharp and Dohme	No comments.	No action required.
	Pfizer	No comments.	No action required.
	Roche Products	No comments.	No action required.
	National Rheumatoid Arthritis Society	No comments.	No action required.
The technology/ intervention	UCB Pharma	*Is the description of the technology or technologies accurate?* Yes.	No action required.

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	AbbVie	No comments.	No action required.
	Bristol-Myers Squibb	No comments.	No action required.
	Merck Sharp and Dohme	No comments.	No action required.
	Pfizer	No comments.	No action required.
	Roche Products	No comments.	No action required.
	National Rheumatoid Arthritis Society	No comments.	No action required.
Population	UCB Pharma	Is the population defined appropriately? Yes.	No action required.
	Bristol-Myers Squibb	The population is not properly defined - the description 'whose disease has not responded adequately' does not explicitly state how response is assessed (which clinical measure is used) and could lead to ambiguity.	Comment noted. The wording of the scope reflects the marketing authorisation for certolizumab pegol. NICE technology appraisal 130 (Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis) defined 'adequate response' as an improvement in Disease Activity Score 28 (DAS28) of 1.2 points or more. Attendees at the scoping workshop observed that the ongoing update of TA130 could potentially adopt a different criterion. Attendees at the scoping workshop agreed that the scope should use a broad description of the population, so that the Appraisal Committee is free to choose a precise definition that reflects the

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			evidence and the published NICE guidance at the time of the appraisal. No action required.
	Pfizer	Pfizer consider that the population under evaluation, i.e., moderate to severe rheumatoid arthritis, does not align with previous NICE recommendations on the use of biologic DMARDs after the failure of a TNF inhibitor (TA195) [1]. Therefore, Pfizer suggest that NICE consider an amendment to include only severe patients in the scope of this appraisal.	Comment noted. The wording of the draft scope reflects the marketing authorisation for certolizumab pegol. No action required.
	AbbVie	No comments.	No action required.
	Merck Sharp and Dohme	No comments.	No action required.
	Roche Products	No comments.	No action required.
	National Rheumatoid Arthritis Society	No comments.	No action required.
Comparators	UCB Pharma	The Draft Scope indicates that one population of interest is: *"For adults previously treated with TNF inhibitors and rituximab:"* in which tocilizumab in combination with methotrexate should be considered as a comparator. We would like to note that the choice of this patient group does not reflect the current NICE commissioning algorithm (May 2013) as no anti-TNFs are recommended in this population. We ask that CZP is evaluated in the same populations as the other anti-TNFs and reflected	Comment noted. During the scoping workshop, attendees advised that there were no data to support the use of certolizumab pegol at this point in the treatment pathway. For this reason, this population has been removed from the scope.

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		in the NICE commissioning algorithm (May 2013).	
	AbbVie	No comments.	No action required.
	Bristol-Myers Squibb	It is feasible that patients in the indicated population could be previously treated with all other biologic DMARDs and be eligible for treatment with tocilizumab - in this case the comparator could be further conventional DMARDs / best supportive care.	Comment noted. During the scoping workshop, clinical and patients experts advised that this group of people would receive best supportive care rather than conventional DMARDs. The scope has been amended to include a comparator of best supportive care.
	Merck Sharp and Dohme	The NICE commissioning algorithm for biologic drugs for the treatment of rheumatoid arthritis recommends rituximab in cases of inadequate response to other biologic therapies. The draft scope suggests that for adults previously treated with other DMARDs including at least 1 TNF inhibitor, certolizumab pegol should be compared with rituximab. The other recommended biologics should also be considered as comparators at this point in the treatment pathway.	Comment noted. In TA195 (Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor), the Committee concluded that rituximab was a cost-effective treatment option for patients with an inadequate response to a TNF-alpha inhibitor. In TA195, the other biologics were recommended only for patients who have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event. No action required.

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		It is not clear whether data exist to support the use of certolizumab pegol for adults previously treated with TNF inhibitors and rituximab. Tocilizumab is suggested as the comparator; the other licensed biologics should also be considered as comparators at this point in the treatment pathway (data permitting).	During the scoping workshop, attendees advised that there were no data to support the use of certolizumab pegol at this point in the treatment pathway. For this reason, this population has been removed from the scope.
		For adults for whom rituximab is contraindicated or withdrawn, tocilizumab should also be included as a comparator (in alignment with the NICE commissioning algorithm).	Tocilizumab has been added to the scope as a comparator.
	Pfizer	Pfizer suggest that inclusion of patients who have failed both a TNF inhibitor and rituximab is potentially inconsistent with populations considered during previous appraisals of TNF inhibitors. Therefore, Pfizer recommend that NICE consider removing this population from the draft scope.	During the scoping workshop, attendees advised that there were no data to support the use of certolizumab pegol at this point in the treatment pathway. For this reason, this population has been removed from the scope.
		For completeness, Pfizer suggest that NICE also consider tocilizumab as a comparator to CZP in the following population: "*For adults for whom rituximab is contraindicated or withdrawn* • *Abatacept, adalimumab, etanercept, golimumab and infliximab each in combination with methotrexate*" This would ensure that this appraisal aligns with both TA195 and TA247, and the NICE RA	Tocilizumab has been added to the scope as a comparator.

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		commissioning algorithm [1, 2]. *[References provided but not reproduced here.]*	
	Roche Products	Tocilizumab monotherapy should be considered a relevant comparator. Tocilizumab is licensed for use as monotherapy and is widely used in the NHS.	Comment noted. In TA247 (Tocilizumab for the treatment of rheumatoid arthritis) the Committee discussed tocilizumab given as monotherapy. It concluded that no evidence for tocilizumab monotherapy within its licensed indication was available, and therefore no recommendations for tocilizumab as a monotherapy could be made (see section 4.6 of TA247). At the scoping workshop, the patient and clinical experts stated that tocilizumab monotherapy may be used. Tocilizumab monotherapy has been added to the scope as a comparator for adults for whom rituximab cannot be given because methotrexate is contraindicated or withdrawn.
	National Rheumatoid Arthritis Society	No comments.	No action required.
Outcomes	UCB Pharma	Reduction in household and work related productivity	Comment noted. The NICE guide to the methods of technology appraisal (2013) states that productivity costs are not included in the economic analyses for a technology appraisal (see section 5.1.10). No action required.

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	AbbVie	No comments.	No action required.
	Bristol-Myers Squibb	No comments.	No action required.
	Merck Sharp and Dohme	No comments.	No action required.
	Pfizer	No comments.	No action required.
	Roche Products	No comments.	No action required.
	National Rheumatoid Arthritis Society	No comments.	No action required.
Economic analysis	UCB Pharma	As other PAS for comparators are not in the public domain we can only speculate on these within our analysis.	Comment noted. Section 3.1.24 of the NICE guide to the processes of technology appraisal (2014) states that NICE will not share confidential details of a patient access scheme for a comparator technology. To allow the Committee to explore the impact of using the actual cost of the comparator in the analyses, the company for the new intervention technology should model the cost effectiveness of their technology using a range of potential discounts for the comparator.
	AbbVie	No comments.	No action required.
	Bristol-Myers Squibb	No comments.	No action required.
	Merck Sharp and Dohme	No comments.	No action required.
	Pfizer	No comments.	No action required.
	Roche Products	No comments.	No action required.

Section	Consultee/ Commentator	Comments	Action
	National Rheumatoid Arthritis Society	No comments.	No action required.
Equality and Diversity	UCB Pharma	No comments.	No action required.
	AbbVie	No comments.	No action required.
	Bristol-Myers Squibb	No comments.	No action required.
	Merck Sharp and Dohme	No comments.	No action required.
	Pfizer	No comments.	No action required.
	Roche Products	No comments.	No action required.
	National Rheumatoid Arthritis Society	No comments.	No action required.
Innovation	UCB Pharma	No comments.	No action required.
	AbbVie	No comments.	No action required.
	Bristol-Myers Squibb	No comments.	No action required.
	Merck Sharp and Dohme	No comments.	No action required.
	Pfizer	No comments.	No action required.
	Roche Products	No comments.	No action required.
	National Rheumatoid Arthritis Society	No comments.	No action required.
Other considerations	UCB Pharma	We ask for clarification on the foundation of the interest in the following subgroups - sero-negative and sero-positive - people identified as having had primary	The subgroups were included because they were in the scope for TA195 (Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment

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		or secondary failure of response to the first TNF inhibitor.	of rheumatoid arthritis after the failure of a TNF inhibitor). Attendees at the scoping workshop for certolizumab pegol agreed that the response to biological DMARDs may vary between people with seronegative and seropositive antibody status, and between people with primary and secondary failure of response. Attendees at the scoping workshop agreed that it was appropriate to include these subgroups in the scope. No action required.
	AbbVie	No comments.	No action required.
	Bristol-Myers Squibb	No comments.	No action required.
	Merck Sharp and Dohme	No comments.	No action required.
	Pfizer	No comments.	No action required.
	Roche Products	No comments.	No action required.
	National Rheumatoid Arthritis Society	No comments.	No action required.
NICE Pathways	UCB Pharma	No comments.	No action required.
	AbbVie	No comments.	No action required.
	Bristol-Myers Squibb	No comments.	No action required.
	Merck Sharp and Dohme	No comments.	No action required.
	Pfizer	No comments.	No action required.
	Roche Products	No comments.	No action required.

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	National Rheumatoid Arthritis Society	No comments.	No action required.
Questions for consultation	Merck Sharp and Dohme	Biosimilar infliximab has a marketing authorisation for psoriatic arthritis and will be marketed in the UK from the 25th February 2015.	Comment noted. Biosimilars of infliximab are included in the scope and their availability will be taken into account during the appraisal in line with the Institute's position statement on biosimilars.
	UCB Pharma	No comments.	No action required.
	AbbVie	No comments.	No action required.
	Bristol-Myers Squibb	No comments.	No action required.
	Pfizer	No comments.	No action required.
	Roche Products	No comments.	No action required.
	National Rheumatoid Arthritis Society	No comments.	No action required.
Additional comments on the draft scope	Merck Sharp and Dohme	NICE decided not to proceed with a proposed review of existing guidance for rheumatoid arthritis (sequential treatment - after failure of disease-modifying anti-rheumatic drugs including a TNF-inhibitor) until the current ongoing MTA of first-line biologic therapies concluded. Given the proposed scope, it may now be appropriate for NICE to re-evaluate this decision.	Comment noted. Having consulted on this topic and taking into account the review decision for TA195, TA225 and TA247, the Institute decided that a single technology appraisal of certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF inhibitor was appropriate..

Appendix D – NICE's response to comments on the draft scope and provisional matrix

The following consultees/commentators indicated that they had no comments on the draft remit and the draft scope

British Society of Rehabilitation Medicine
Department of Health
Royal College of Nursing
Royal College of Pathologists

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Equalities National Council	PIP		Remove	The Equalities National Council have narrowed their remit and have been removed for the matrix under 'patient groups'
2.	British Society for Paediatric and Adolescent Rheumatology	NICE Secretariat		Remove	The technology is licensed for adults therefore the British Society for Paediatric and Adolescent Rheumatology is not an appropriate to include