

Certolizumab pegol for treating rheumatoid arthritis after an inadequate response to a TNF-alpha inhibitor

Single Technology Appraisal

2nd meeting: 10th August 2016

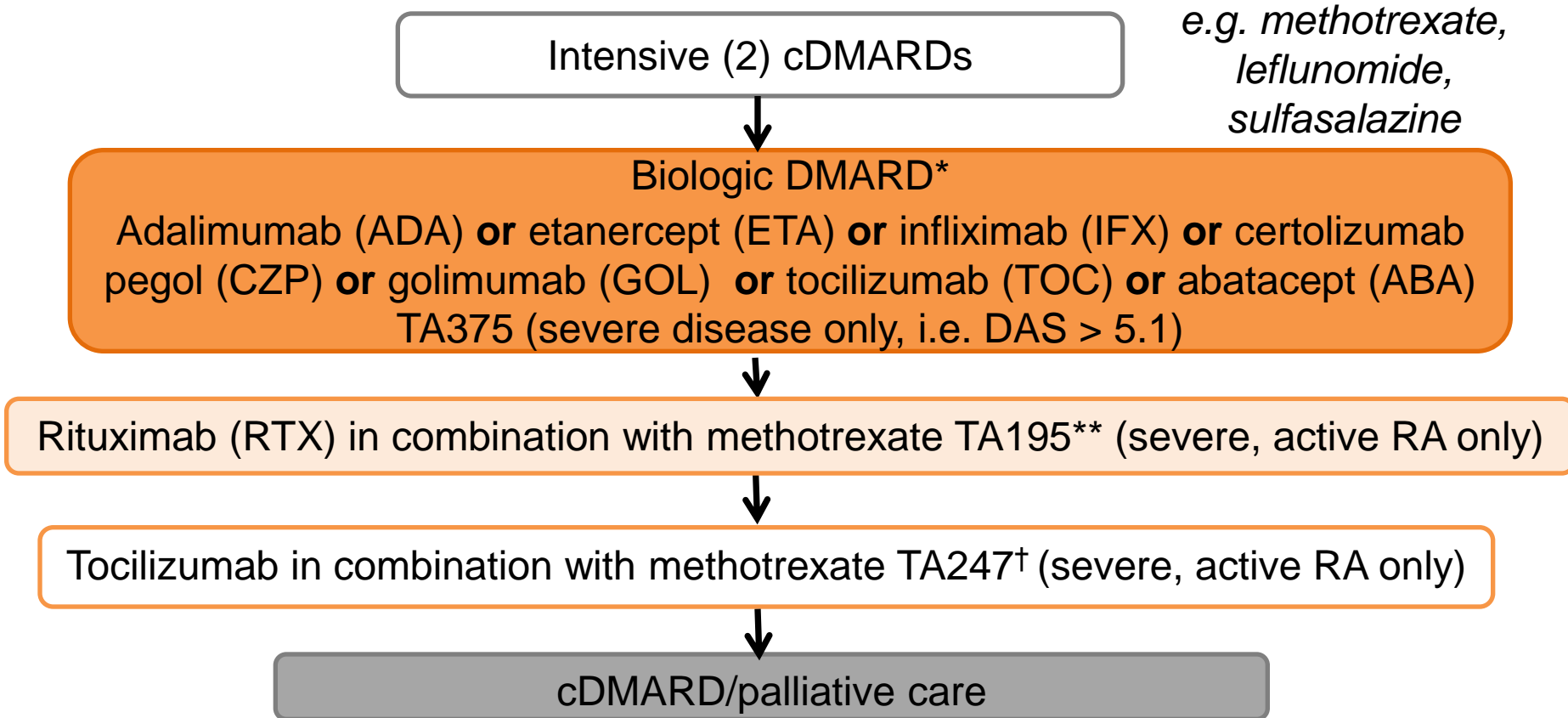
1st meeting: 15th June 2016

Committee C

Certolizumab pegol (Cimzia, UCB Pharma)

- Solution for injection administered subcutaneously
- List price for 200mg pre-filled syringe is £357.50 (BNF)
- Agreed PAS provides 1st 12 weeks of therapy free to NHS
- Annual cost of £6793 with first year PAS and £9295 per year thereafter
- Holds a marketing authorisation for:
 - Treatment of moderate to severe active RA in adults when response to DMARDs (including methotrexate) has been inadequate
 - As monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate
 - Treatment of severe, active and progressive RA in adults not previously treated with methotrexate or other DMARDs
 - MA Extension: treatment of moderate and severe RA whose disease has responded inadequately to a TNF-alpha inhibitor

Treatment pathway for RA



- *Certolizumab pegol, etanercept, adalimumab or tocilizumab monotherapy if methotrexate (MTX) is inappropriate (TA375); adalimumab or etanercept monotherapy after initial failure with TNFi (TA195)
- **If rituximab is contraindicated or withdrawn due to adverse events then the following can be used: adalimumab or etanercept or infliximab or abatacept all in combination with MTX (TA195) or golimumab in combination with MTX (TA225)
- †Would not be used if tocilizumab has been used previously in the sequence

NICE scope

Pop.	Adults with moderate to severe, active rheumatoid arthritis whose disease has not responded adequately to a TNF inhibitor
Int.	Certolizumab pegol (CZP) monotherapy or in combination with methotrexate (MTX)
Com.	<p>For adults previously treated with other DMARDs including at least 1 TNF inhibitor</p> <ul style="list-style-type: none">• Rituximab in combination with methotrexate <p>For adults for whom rituximab is contraindicated or withdrawn</p> <ul style="list-style-type: none">• Abatacept, adalimumab, etanercept, golimumab, infliximab and tocilizumab each in combination with methotrexate <p>For adults for whom rituximab therapy cannot be given because methotrexate is contraindicated or withdrawn</p> <ul style="list-style-type: none">• Adalimumab monotherapy, etanercept monotherapy or tocilizumab monotherapy <p>For people with moderate to severe, active disease despite treatment with biological DMARDs recommended according to NICE guidance</p> <ul style="list-style-type: none">• Best supportive care

Company's decision problem

Pop.	Adults with moderate to severe active RA whose disease has not responded adequately to a tumour necrosis factor inhibitor (TNFi). Moderate to severe disease activity defined as disease activity score 28 (DAS28) >3.2
Int.	Certolizumab pegol (CZP) monotherapy or in combination with methotrexate (MTX)
Com.	<p>Treatment sequences are used:</p> <p>Population A - adults previously treated with other DMARDs including at least 1 TNFi: CZP is inserted into the sequence before rituximab (RTX) in combination with MTX</p> <p>Population B - adults for whom RTX is contraindicated or withdrawn: first line of therapy is either CZP or one of the other comparators in the scope: abatacept (ABA), adalimumab (ADA), etanercept (ETA), golimumab (GOL), infliximab (IFX) and tocilizumab (TOC) each in combination with MTX</p> <p>Population C - adults for whom RTX therapy cannot be given because MTX is contraindicated or withdrawn: first line of therapy in the sequence is either CZP, ADA, ETA or TOC, all as monotherapy</p>

Company's original base case results: People for whom rituximab is a treatment option

Sequences	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER (£/QALY)	Probability (%) of cost effectiveness at a threshold of	
						£20,000/QALY	£30,000/QALY
DETERMINISTIC RESULTS:							
RTX	7.000	£138,520	-	-	-	-	-
CZP before RTX	7.286	£148,361	0.286	£9,842	£34,378	-	-
PROBABILISTIC RESULTS:							
RTX	7.031	£139,933	-	-	-	97.80	63.02
CZP before RTX	7.321	£149,579	0.290	£9,647	£33,222	2.20	36.98

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year; CZP, certolizumab pegol; RTX, rituximab.

Source Company's submission

ERG preferred base case results: People for whom rituximab is a treatment option (not including confidential comparator PAS for tocilizumab)

Sequences	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER (£/QALY)	Probability (%) of cost-effectiveness at a threshold of	
						£20,000/QALY	£30,000/QALY
DETERMINISTIC RESULTS:							
CZP instead of RTX	7.719	£125,364	-	-	Dominated	-	-
CZP before RTX	8.239	£133,780	-	-	Dominated	-	-
RTX	8.378	£122,451	-	-	-	-	-
CZP after RTX	8.649	£130,016	0.271	£7,565	£27,946	-	-
PROBABILISTIC RESULTS:							
CZP instead of RTX	7.796	£128,376	-	-	Dominated	0.00	0.00
CZP before RTX	8.347	£136,751	-	-	Dominated	0.00	0.20
RTX	8.461	£125,189	-	-	-	71.46	45.64
CZP after RTX	8.732	£132,692	0.271	£7,504	£27,700	28.52	54.26

ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year; CZP, certolizumab pegol; RTX, rituximab
Source ERG report

ACD: Preliminary recommendations

- Recommended in combination with methotrexate as an option for treating active rheumatoid arthritis in adults who have had an inadequate response to, or who cannot tolerate, other disease-modifying antirheumatic drugs (DMARDs), including at least 1 tumour necrosis factor-alpha (TNF-alpha) inhibitor, only if:
 - disease is severe, that is, a disease activity score (DAS28) greater than 5.1 and
 - the person cannot have rituximab therapy because rituximab is contraindicated or not tolerated and
 - the company provides certolizumab pegol with the agreed patient access scheme discount
- as monotherapy for people who have had an inadequate response to, or who cannot tolerate, other disease-modifying antirheumatic drugs (DMARDs), including at least 1 tumour necrosis factor-alpha (TNF-alpha) inhibitor and who cannot have rituximab therapy because methotrexate is contraindicated or not tolerated and where the criteria in 1.1 are met.

ACD considerations

The Committee:

- concluded that certolizumab pegol has a similar efficacy to other available bDMARDs
- accepted the analyses for people for whom either rituximab or methotrexate are contraindicated or not tolerated
- for population A (where rituximab is a treatment option), had concerns over sequences of different lengths
- agreed that sequences were missing from the company's base case, particularly *instead of* rituximab + methotrexate
- concluded that certolizumab was not cost effective when all treatment sequences were included

Consultation comments

- Comments received from:
 - Consultees:
 - Company: UCB Pharma (certolizumab pegol)
 - Professional organisation: British Society of Rheumatology (BSR) endorsed by Royal College of Physicians (RCP) and National Rheumatoid Arthritis Society (NRAS)
 - Commentators:
 - Comparator company: Merck, Sharp & Dohme

Comments on ACD: BSR

- Overall supportive of the recommendations
- Highlight that certolizumab is a good option for pregnant women due to the low placental transfer of the drug
- Ask for the threshold of DAS28 $>$ 5.1 to be removed because:
 1. *not consistent with clinical practice: Where patients are non-responders, they are still considered to have severe active RA because their DAS score was $>$ 5.1 before their first bDMARD*
 2. *not consistent with TA195: see next slide*

Reminder of current NICE guidance – consistency in terminology

- TA375 recommends that treatment with the first biologic should only be initiated when disease is **severe**, that is, a DAS28 score of greater than 5.1 and to continue treatment if there is a moderate EULAR response at 6 months
- TA195 recommends that treatment with a second biologic (after first TNFi) should only be initiated if disease is **severe** and active and to continue treatment only if there is an adequate response, defined as a DAS28 improvement of >1.2 at 6 months

Comments from Merck, Sharp & Dohme (commentator)

- Section 4.1 of the ACD only refers to TA195 which does not cover golimumab. TA225 (golimumab after DMARDs) should also be referred to in this section for the purpose of completion
- Inconsistencies in the ERG's scenario analysis as it *'assumes that all TNF-alpha inhibitors have the same efficacy as certolizumab but QALYs associated with golimumab are lower...'*. ERG do not consider the results of the GO-AFTER extension study (reflects significant improvement of golimumab compared to the original study)

Comments on ACD: UCB Pharma

Themes:

- Terminology in ACD re. patient access scheme ('discount' is incorrect as it is a dose-based scheme) & standard text in section 1.6 (those already receiving treatment in the NHS)
- Limiting the recommendation to '*only if disease is severe*'; defined as a DAS28 score of >5.1
- Additional benefits of certolizumab pegol
- Suitability of a fixed-effect network meta-analysis model
- Alternative estimate for the cost effectiveness of certolizumab pegol in people for whom rituximab is a treatment option

UCB comments 1: Moderate to severe disease

- State that eligibility criteria of “severe disease activity” only applies to initiation of first biologic as in TA375, not second biologic
- Restate that the population for the scope is for moderate to severe and as such the wording should reflect this (DAS28>3.2)

UCB comments 2: Additional benefits of certolizumab pegol

- Disagrees that all health-related benefits are captured by the QALY – *workplace and household activity*
- Data from PREDICT study (in submission) supports improvements in productivity following treatment with certolizumab
- Certolizumab pegol has a novel molecular structure – only PEGylated FAB' fragment TNFi
- Off-label evidence that certolizumab pegol may be used during pregnancy

UCB comments 3: Suitability of the fixed-effect network meta analysis (NMA)

- Agrees with ERG that there is heterogeneity between studies but states that there is insufficient information to quantify it
- Conducted a multinomial (rather than a binomial, as in the submission) random effects model and compared it with the original fixed effect model
- Found that the mean effect sizes were similar for both but differed by wide 95% confidence intervals (random effects interval exceeds fixed effect interval)
- Request a change to the ACD; that the heterogeneity *'could lead to an under-estimation of the uncertainty surrounding the effectiveness of certolizumab pegol'*

UCB 4: Alternative assumptions and additional treatment sequences - people for whom rituximab is a treatment option

- Company used ERG's preferred model with the following modifications to the assumptions:
 - Equal treatment discontinuation of rituximab, tocilizumab and certolizumab (i.e. equal rates as in original base case)
 - A six monthly re-treatment interval maintained as in the original base case
- Included 3 sequences
 - Rituximab
 - Certolizumab before rituximab
 - Certolizumab instead of rituximab (not previously in base case)

UCB revised base case results

Sequences	Total cost	Total QALY	Incr. cost	Incr. QALY	ICER versus reference
RTX + MTX	£119,814	7.266	-	-	
CZP+MTX instead of RTX+MTX	£123,281	7.293	£3,467	0.03	£130,382
CZP+MTX before RTX+MTX	£130,577	7.685	£10,763	0.42	£25,682

Source Company's ACD response

Company comments that the cost effectiveness conclusion varies when different assumptions for treatment durations for TNFis and non TNFis are used in the model

Company: treatment duration (rate of discontinuation) for biologics

Base case assumed **same** for all biological treatments (15.6% discontinuation at 6 months) based on BSRBR

Undertaken sensitivity analysis on revised base case using:

- Ramiro et al (2015): USA (n = 988 TNFi, 109 non-TNFi). Annual discontinuation rate of 19% on TNFis, 38% on non-TNFis i.e longer treatment duration on TNFis
- Du Pan et al (2012): Switzerland (n = 853 TNFi, 632 non-TNFis). Discontinuation hazard ratio 0.50 for non-TNFis compared to TNFis i.e longer treatment duration on non-TNFis

ERG assumed longer mean treatment duration for rituximab (11.31 years) than TNFis (4.06 years) - from TA195 (At 6 months: TNFi 11.6%, rituximab 4.3%, aba/toci 7.8%)

- Company considers this lacks clinical plausibility as it was taken from long term extension of REFLEX (rituximab) trial and would not reflect clinical practice
- Company comments that this is inconsistent with assumptions made by Assessment Group in TA375 (dependent on response status, not treatment)

Company conclusion: contradictory evidence supports assumption of equal treatment duration

BSRBR: British Society of Rheumatology Biologics Register

Company: rituximab retreatment interval

Base case assumed retreatment with rituximab every **6** months

- SmPC for rituximab: *“The need for further courses should be evaluated 24 weeks following the previous course. Retreatment should be given at that time if residual disease activity remains, otherwise retreatment should be delayed until disease activity returns”*

ERG base case used rituximab retreatment interval of **7.35** months

- The Appraisal Committee for TA195 concluded that the average retreatment interval was between 6 and 8.7 months. 7.35 is midpoint between these two figures

Company revised base case assumes **6** months but sensitivity analyses performed using 7.35 months

Company revised base case and sensitivity analyses

Analysis	Duration of treatment	Re-treatment interval	CZP instead of RTX ICER	CZP before RTX ICER
Company's revised base case	Equal for all bDMARDs (mean: 4.06 years)	6 months	£130,382 (extendedly dominated)	£25,682
Assuming longer duration on TNFis	Ramiro et al TNFi 19% non-TNFi: 38%	6 months	£16,230	£17,293
Assuming longer duration on non-TNFis	Du Pan et al Hazard ratio of 0.5 for non-TNFi compared with TNFi	6 months	Saving of £4,698 per QALY lost (south west quadrant)	Dominated
Equal duration, but longer retreatment interval	Equal for all bDMARDs (mean: 4.06 years)	7.35 months	£291,331	£30,411
Longer duration on TNFis and longer ritux retreatment interval	Ramiro et al TNFi 19% non-TNFi: 38%	7.35 months	£20,571	£18,485

ERG's critique of company's ACD response: treatment duration

- Ramiro and Du Pan are both observational studies that compare TNFis with non-TNFis
- Grouping rituximab, tocilizumab and abatacept together may result in inaccurate estimate for rituximab
- Only 39% patients in Ramiro received non-TNFi
- Ramiro study acknowledges the differences between European and American patients (different prescription patterns, reimbursement policies, patients' comorbidities)
- Assumptions in TA195 and TA375 were different – can't be consistent with both
- ERG acknowledges risk of bias of a trial overestimating treatment duration compared to clinical practice
- However, REFLEX study (used in TA195) most accurate source of data as it reported the retreatment of rituximab, rather than non-TNFis
- Uncertainty explored in scenario analysis

ERG's critique of company's ACD response: rituximab retreatment interval

- ERG does not concur that the SmPC for rituximab justifies a retreatment interval of 6 months
- Identified evidence from SUNRISE trial
 - 1 versus 2 courses of rituximab in RA patients with a previous inadequate response to 1 or more TNFis
 - Showed that 2 courses of rituximab over 48 weeks result in higher ACR20 response compared with a single course
- ERG now consider the retreatment interval should be mean from REFLEX trial (10.09 months)
- 10.09 months is closer to the 9 month retreatment interval assumed in TA375

ACR: American College Rheumatology

ERG revised base case

As company revised base case with:

- treatment duration as per TA195 (unchanged from ERG report)
- rituximab retreatment interval of 10.09 months

Sequences	Total QALY	Total cost (£)	Incr. QALY	Incr. cost (£)	ICER (£/QALY)
RTX + MTX	8.148	117,272	-	-	
CZP+MTX instead of RTX+MTX	7.444	129,746	-	-	Dominated
CZP+MTX before RTX+MTX	8.047	131,106	-	-	Dominated

Source ERG critique of ACD response

ERG scenario analyses in response to company's comments at ACD consultation

	Duration of treatment	Re-treatment interval (months)	CZP instead of RTX ICER	CZP before rituximab ICER
ERG revised base case	Mean durations: TNFi: 4.06 years rituximab: 11.31 years tocilizumab: 6.17 years (TA195)	10.09 (REFLEX study)	Dominated	Dominated
ERG scenario analysis	Equal for all bDMARDs (mean: 4.06 years)	10.09 (REFLEX study)	£485,388 (extendedly dominated)	£36,113
ERG scenario analysis	Equal for all bDMARDs (mean: 4.06 years)	9 (TA375)	£422,474 (extendedly dominated)	£34,265

Key issues

- Is a recommendation for a moderate disease population (for which the comparator would not be biologic) possible?
- What is the most plausible ICER for people for whom rituximab is a treatment option?
 - Treatment duration
 - Retreatment interval with rituximab
- Innovation
- Equalities – cert peg can be used in pregnancy
- PPRS