Certolizumab pegol for the treatment of rheumatoid arthritis

This guidance was developed using the single technology appraisal process
Certolizumab pegol for the treatment of rheumatoid arthritis

Ordering information

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- The NICE guidance (this document).
- A quick reference guide – the recommendations.
- ‘Understanding NICE guidance’ – a summary for patients and carers.
- Details of all the evidence that was looked at and other background information.

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- N2106 (quick reference guide)
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1 Guidance

1.1 Certolizumab pegol is recommended as an option for the treatment of people with rheumatoid arthritis only if:

- certolizumab pegol is used as described for other tumour necrosis factor (TNF) inhibitor treatments in ‘Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis’ (NICE technology appraisal guidance 130) and
- the manufacturer provides the first 12 weeks of certolizumab pegol (10 pre-loaded 200-mg syringes) free of charge to all patients starting treatment.

1.2 When using the DAS28 (as set out in NICE technology appraisal guidance 130), healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person’s responses to the DAS28 and make any adjustments they consider appropriate.

2 The technology

2.1 Certolizumab pegol (Cimzia, UCB Pharma) is TNF-α-specific Fab fragment of a humanised monoclonal antibody. It binds with high affinity to both soluble and membrane-bound TNF-α, thereby inhibiting TNF-α activity. Certolizumab pegol is one of a group of treatments known as biological disease-modifying anti-rheumatic drugs (DMARDs). Certolizumab pegol in combination with methotrexate is indicated for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to conventional DMARDs including methotrexate, has been inadequate. Certolizumab pegol can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. The summary of product characteristics (SPC) states that the recommended starting dose for adults with rheumatoid arthritis is 400 mg subcutaneously at weeks 0, 2 and 4, followed by maintenance doses of 200 mg
subcutaneously every 2 weeks. The SPC also states that continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit in the first 12 weeks of treatment.

2.2 According to the SPC, contraindications for the use of certolizumab pegol are: hypersensitivity to the active substance; active, severe infections (including tuberculosis, sepsis and opportunistic infections); and severe heart failure. For full details of side effects and contraindications, see the summary of product characteristics.

2.3 The cost to the NHS of certolizumab pegol is £715 for two 1-ml syringes, each containing 200 mg of certolizumab pegol (MIMS December 2009). The cost for the first year, including loading doses, is £10,367.50 with an annual cost thereafter of £9295. Costs may vary in different settings because of negotiated procurement discounts.

2.4 The manufacturer has agreed a patient access scheme with the Department of Health. Under the scheme, people receive the first 12 weeks of therapy (currently 10 pre-loaded syringes of 200 mg each) of certolizumab pegol free of charge. The scheme will be managed by a homecare provider with alternative arrangements for hospitals who initially treat patients in the hospital or hospitals that do not use a homecare provider. The manufacturer has stated that this patient access scheme will be available to the NHS at least until this guidance is reviewed by NICE. The Department of Health has agreed that NICE can consider the patient access scheme.
3 The manufacturer’s submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of certolizumab pegol and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer approached the decision problem by considering certolizumab pegol both as monotherapy and in combination with methotrexate for the treatment of rheumatoid arthritis after the failure of conventional DMARDs. The manufacturer identified two possible comparators for certolizumab pegol monotherapy: etanercept and adalimumab. The manufacturer identified five possible comparators for certolizumab pegol in combination with methotrexate: etanercept plus methotrexate, adalimumab plus methotrexate, rituximab plus methotrexate, infliximab plus methotrexate and tocilizumab plus methotrexate. The main outcome reported in the submission was American College of Rheumatology criteria 20 (ACR20), 50 (ACR50), and 70 (ACR70) response at 3 and 6 months.

3.2 The manufacturer identified three randomised controlled trials (RCTs) that met the criteria for inclusion in the review. These were two parallel-group studies comparing 400 mg or 200 mg certolizumab pegol plus methotrexate every 2 weeks with placebo plus methotrexate (RAPID 1 [n = 982] and RAPID 2 [n = 619]), and a parallel-group study (n = 220) comparing 400 mg certolizumab pegol every 4 weeks with placebo (FAST4WARD). The primary outcome in all three studies was the ACR20 response at week 24. This is defined as at least a 20% improvement in both the tender joint count and the swollen joint count and at least a 20% improvement in three of the other five core set measures included in the ACR score. All the trials were in people who had had active rheumatoid arthritis (according to American College of Rheumatology criteria) for more than 6 months. In the RAPID 1 and
RAPID 2 trials patients had to have active rheumatoid arthritis despite treatment with methotrexate. In the FAST4WARD trial patients had to have active disease where treatment with one or more DMARDs had failed because of lack of efficacy or intolerance. The manufacturer explained that although the eligibility criteria for the RAPID trials did not include failure of treatment with a conventional DMARD, the average number of DMARDs previously received by the trial participants was 1.2 to 1.4 (not including methotrexate). In the FAST4WARD trial people were excluded if they had previously received treatment with a TNF inhibitor. In the RAPID trials people were excluded if previous treatment with a TNF inhibitor had failed. Less than 4% of people in the RAPID trials had previously received a TNF inhibitor.

3.3 All three RCTs found that a statistically significantly greater proportion of people had an ACR20 response at 24 weeks with certolizumab pegol than with the comparators. There were no statistically significant differences in the proportion of people with an ACR20 response at 24 weeks between the two certolizumab pegol dosage regimens in the RAPID 1 and RAPID 2 trials.

3.4 The manufacturer undertook a meta-analysis of the results of the RAPID 1 and RAPID 2 trials. Statistical heterogeneity was detected for some outcomes (using Cochrane’s $\chi^2$ test) and so both fixed- and random-effects models were used. The analysis found that people receiving certolizumab pegol plus methotrexate were five times as likely to achieve an ACR20 response at 24 weeks as people given placebo plus methotrexate.

3.5 The manufacturer stated that there were no trials that included all treatment options. In the submission a series of indirect treatment comparison meta-analyses were carried out to assess the relative effectiveness of adalimumab, tocilizumab, etanercept, infliximab, rituximab, certolizumab pegol and methotrexate. The indirect comparison analysis used results from 13 trials for the combination...
therapies, 10 of which contributed to the analysis of ACR response at 6 months and 7 of which contributed to the analysis of ACR response at 3 months. The results of five monotherapy trials were used in a separate indirect comparison analysis. All five were used in the analysis of ACR response at 3 months, and four were used in the analysis of ACR response at 6 months.

3.6 Seven trials (two of certolizumab pegol, one of adalimumab, two of etanercept, one of infliximab and one of tocilizumab) were included in the analysis that evaluated ACR response at 3 months for treatment used in combination with methotrexate. No statistically significant differences were identified between certolizumab pegol and any of the other treatments for ACR20 or ACR50 response. However, there were statistically significantly greater odds of achieving ACR70 response at 3 months with certolizumab pegol plus methotrexate than with tocilizumab plus methotrexate.

3.7 Ten trials (two of certolizumab pegol, three of adalimumab, one of etanercept, two of infliximab, one of rituximab and one of tocilizumab) were included in the analysis that evaluated ACR response at 6 months for treatment used in combination with methotrexate. A statistically significantly higher proportion of people achieved an ACR20, 50 and 70 response at 6 months with certolizumab pegol plus methotrexate than with infliximab plus methotrexate. A statistically significantly higher proportion of people achieved an ACR20 response at 6 months with certolizumab pegol plus methotrexate than with tocilizumab plus methotrexate. There were no other statistically significant differences, suggesting that most of the biological DMARDs looked at had similar efficacy for ACR response at 6 months.

3.8 Four trials (two of adalimumab, and one each of certolizumab pegol and etanercept) were included in each of two analyses that evaluated ACR response at 3 and 6 months for treatments used as monotherapy. No statistically significant differences between
certolizumab pegol and any of the other comparator treatments were identified for ACR20, ACR50 or ACR70 response at 3 or 6 months.

3.9 The manufacturer submitted two versions of its economic model (the original model and a revised model that was produced in response to requests for clarification from NICE). The revised model differed from the original model in three key ways: assumptions used for utilities, adverse events and discontinuation probabilities. Both models included scenarios with and without the patient access scheme.

3.10 The models were Markov-based models that used a hypothetical cohort of people with moderate to severe active rheumatoid arthritis, whose disease had responded inadequately to conventional DMARDs, including methotrexate. The models were designed to compare certolizumab pegol plus methotrexate with etanercept plus methotrexate, adalimumab plus methotrexate, rituximab plus methotrexate, and infliximab plus methotrexate. The models assumed certolizumab pegol therapy would continue if there was an adequate ACR response (ACR20 or greater) 6 months after starting therapy. They also assumed that if there was intolerance to certolizumab pegol therapy within 6 months, an alternative TNF inhibitor would be given. Differing cycle lengths were applied in the first three model cycles, no half-cycle correction was applied after the first cycle, and the model had a 45-year time horizon.
3.11 In the models, the effectiveness estimates for certolizumab pegol and the comparator treatments were derived from the indirect comparison meta-analysis. The effectiveness estimates were calculated by:

- combining ACR20, ACR50 and ACR70 responses from the trial control arms (methotrexate for combined therapy, and placebo for monotherapy) to provide baseline estimates of ACR response without biological DMARDs and
- applying the approximate odds ratio from the indirect comparison analysis to this baseline in order to estimate ACR20, ACR50 and ACR70 responses separately for people receiving biological DMARDs.

3.12 The manufacturer’s original model contained the following utility assumptions:

- a baseline utility value of 0.38
- an initial increase in utility as a result of treatment dependent on ACR response
- an annual decrease in utility while on biological treatment of 0.037 if response had been assessed at 6 months (or 0.014 if assessed at 3 months)
- a loss of the initial increase in utility when treatment is stopped
- an annual decrease in utility of 0.037 after stopping biological treatment and starting treatment with conventional DMARDs.

The revised model assumed an annual increase in utility while on biological treatment of 0.0202 if response had been assessed at 6 months (or 0.0402 if assessed at 3 months), and an annual decrease in utility of -0.0025 while on treatment with conventional DMARDs.

3.13 The original model base case (not including the patient access scheme) reported that when etanercept plus methotrexate was compared with certolizumab pegol plus methotrexate, the QALY
gain was -0.005 and incremental costs were £2675. This meant that certolizumab pegol plus methotrexate was less effective and more costly than etanercept plus methotrexate. When certolizumab pegol plus methotrexate was compared with adalimumab plus methotrexate, the QALY gain was 0.102 and incremental costs were £3563, giving an incremental cost-effectiveness ratio (ICER) for certolizumab pegol of £34,930 per quality-adjusted life year (QALY) gained. Certolizumab pegol plus methotrexate compared with infliximab plus methotrexate showed a QALY gain of 0.211 and incremental costs of -£4468, meaning that certolizumab pegol plus methotrexate dominated infliximab plus methotrexate (that is, certolizumab pegol plus methotrexate was more effective and less costly than infliximab plus methotrexate). Certolizumab pegol monotherapy compared with adalimumab monotherapy resulted in a QALY gain of 0.127 and incremental costs of £5347. This gave an ICER for certolizumab pegol of £42,197 per QALY gained. When etanercept monotherapy was compared with certolizumab pegol monotherapy, the QALY gain was -0.047 and incremental costs were -£297, resulting in an ICER of £6341 per QALY gained for etanercept compared with certolizumab pegol.

3.14 The original model base case (including the patient access scheme) reported that when etanercept plus methotrexate was compared with certolizumab pegol plus methotrexate, the QALY gain was -0.005 and incremental costs were -£900. This meant that certolizumab pegol plus methotrexate was less effective and less costly than etanercept plus methotrexate. The model showed that certolizumab pegol plus methotrexate dominated adalimumab plus methotrexate and infliximab plus methotrexate. The incremental QALY gains were 0.102 and 0.211, and the incremental costs were -£12 and -£8043 respectively. Certolizumab pegol monotherapy compared with adalimumab monotherapy showed a QALY gain of 0.127 and incremental costs of £1772, resulting in an ICER for certolizumab pegol of £13,982 per QALY gained. When etanercept
monotherapy was compared with certolizumab pegol monotherapy, the QALY gain was -0.047 and incremental costs were -£3872, resulting in an ICER of £82,695 per QALY gained for etanercept compared with certolizumab pegol.

3.15 The revised model base case (not including the patient access scheme) reported that when etanercept plus methotrexate was compared with certolizumab pegol plus methotrexate, the QALY gain was 0.065 and incremental costs were £2993, resulting in an ICER for certolizumab pegol of £46,192 per QALY gained. When certolizumab pegol plus methotrexate was compared with adalimumab plus methotrexate, the QALY gain was 0.242 and incremental costs were £3124, resulting in an ICER for certolizumab pegol of £12,937 per QALY gained. Certolizumab pegol plus methotrexate compared with infliximab plus methotrexate showed a QALY gain of 0.458 and incremental costs of -£6441, meaning that certolizumab pegol plus methotrexate dominated infliximab plus methotrexate. Certolizumab pegol monotherapy compared with adalimumab monotherapy gave a QALY gain of 0.215 and incremental costs of £1223, resulting in an ICER for certolizumab pegol of £5687 per QALY gained. When etanercept monotherapy was compared with certolizumab pegol monotherapy, the QALY gain was -0.130 and incremental costs were -£517, meaning that certolizumab pegol plus methotrexate was less effective and less costly than etanercept plus methotrexate.

3.16 The revised economic model (including the patient access scheme) reported that certolizumab pegol plus methotrexate dominated etanercept plus methotrexate, adalimumab plus methotrexate and infliximab plus methotrexate. The incremental QALY gains were 0.065, 0.242 and 0.458 respectively and incremental costs were -£582, -£451 and -£10,016 respectively. Certolizumab pegol monotherapy also dominated adalimumab monotherapy with a
QALY gain of 0.215 and incremental costs of -£2352. When etanercept monotherapy was compared with certolizumab pegol monotherapy, the QALY gain was -0.130 and incremental costs were -£4092, resulting in an ICER of £31,582 per QALY gained for etanercept compared with certolizumab pegol.

3.17 Univariate sensitivity analysis of the revised model demonstrated that the model was most sensitive to variation in the time horizon and assumptions around changes in utility during treatment.

3.18 The ERG reviewed the evidence submitted on clinical and cost effectiveness. The ERG considered that the FAST4WARD and RAPID 1 and 2 trials were of acceptable methodological quality and clearly showed that therapy with certolizumab pegol plus methotrexate was more effective than placebo plus methotrexate, and that certolizumab pegol monotherapy was more effective than placebo. However, the ERG noted that although the average number of DMARDs previously taken by participants entering the three certolizumab pegol trials was greater than two, it was unclear from the submission what proportion of participants had taken fewer than two DMARDs. The influence of this on the estimates of effectiveness was difficult to judge.

3.19 The ERG highlighted a number of concerns about the methodology used for the indirect comparison meta-analysis:

- The appropriateness of using an indirect treatment comparison in which only multiple two-way comparisons between biological DMARDs was possible, rather than using a mixed-treatment comparison.
- The method used for selecting the studies to be included in the indirect treatment comparison was unclear. It was possible that relevant information from several excluded studies, including one of certolizumab pegol plus methotrexate versus placebo plus methotrexate (the C87014 trial), could have been used.
• The inclusion of data from the included studies was not consistent.
• There was insufficient consideration and exploration of underlying heterogeneity among the studies included in the indirect comparison meta-analysis.
• Of the 10 trials used in the manufacturer’s indirect comparison meta-analyses for combination therapy, participants in the two certolizumab pegol trials at 6 months had a low previous exposure to DMARDs compared with participants in trials of comparator treatments. Also, the mean methotrexate dosage at the time of entry to the 10 trials was lowest in the certolizumab pegol trials.

3.20 The ERG reviewed the revised economic model. It said that the method of incorporating effectiveness of comparator treatments in the model underestimated uncertainty, was susceptible to the influence of confounding, and may have been biased in favour of certolizumab pegol. The ERG was also concerned about the validity of the utility estimates in the model. The manufacturer’s submission did not provide exact details on how many patients were given health-related quality-of-life questionnaires and the response rates to the questionnaires. The use of mapping approaches to estimate utility scores led to a significant degree of uncertainty in the results, and it was not clear in the manufacturer’s submission how this uncertainty was captured in the model. The utility estimates used were based on the disease and not the treatment, so all patients regardless of treatment attracted the same utility scores, except when treatment response was greater. The ERG was also unable to carry out an independent sensitivity analysis because of programming errors in the model.

3.21 After the first Committee meeting, the Committee requested that the manufacturer provide further details of the C87014 trial (n = 247) that had been excluded from the indirect comparison
meta-analysis. It also asked for an estimate of clinical effectiveness relative to other TNF inhibitors by providing a mixed-treatment comparison that included the trials from the original indirect comparison analysis and the further studies identified by the ERG. The Committee requested that the manufacturer provide further explanation of the revisions made to the original model, specifically the rationale for changes in the assumptions about utility (see section 3.12) and the difference in the total cost estimates between the original and revised models, which were approximately £10,000 lower for certolizumb pegol and each comparator in the revised model. The Committee also requested that the manufacturer explore modelling ACR response, incorporating an assumed constant relationship, and provide an incremental cost-effectiveness analysis with probabilistic sensitivity analysis. Univariate sensitivity analyses were requested using a lower estimate of the cost of infusing the comparator treatments than had been used in the original submission.

3.22 The manufacturer provided additional results from the C87014 study, which compared certolizumab pegol (400 mg monthly) plus methotrexate with placebo plus methotrexate. A statistically significantly greater proportion of people had an ACR20 and ACR50 response at 24 weeks with certolizumab pegol plus methotrexate than with placebo plus methotrexate. ACR 20, 50 and 70 response rates in the certolizumab pegol group were 46%, 18% and 0% respectively. The corresponding values in the placebo group were 23%, 6% and 2%.

3.23 The manufacturer clarified that the utility estimates in the original model were based on what they considered to be an incorrect assumption – that after 6 months of treatment there would be a gradual loss of utility of 0.037 per year. The trial results for certolizumab suggested that Health Assessment Questionnaire score improved while on treatment, which when mapped to EQ-5D
suggested a gain in utility of 0.0202 per year after 6 months of treatment. The manufacturer also explained that a further amendment was made to the change in utility while on follow-on treatment. The annual decrease in utility of -0.037 assumed in the original submission was revised to -0.0025 per year to standardise this with the value used in ‘Rituximab for the treatment of rheumatoid arthritis’ (NICE technology appraisal guidance 126). The manufacturer further explained that on stopping treatment it was assumed that 100% of the initial benefit was lost, but that this was immediately replaced by the treatment response to the follow-on treatments. The change in costs and utilities between the original and revised economic models was explained by the costs of rheumatoid arthritis (for example, hospitalisation) being related to Health Assessment Questionnaire score, so people with worse Health Assessment Questionnaire score and lower utility incurred more costs.

3.24 The manufacturer provided a mixed-treatment comparison that included the studies from the original indirect comparison meta-analysis, the C87014 study, and two studies that both compared etanercept plus methotrexate directly with infliximab plus methotrexate. The manufacturer demonstrated that when using the mixed-treatment comparison methodology instead of the indirect comparison meta-analysis the point estimates of ACR20, 50 and 70 did not change significantly but the uncertainty around the estimates increased.

3.25 Including the C87014 study and two further trials that compared etanercept plus methotrexate with infliximab plus methotrexate in a mixed treatment comparison analysis changed the ACR20, 50 and 70 response rates used in the economic model. For certolizumab pegol plus methotrexate the ACR20, 50 and 70 response rates changed from 77%, 49% and 28% to 69%, 39% and 21% respectively. For etanercept plus methotrexate these changed from
69%, 66% and 31% to 61%, 68% and 43%. For adalimumab plus methotrexate these changed from 61%, 42% and 20% to 62%, 39%, 14%. For infliximab plus methotrexate these changed from 48%, 26% and 11% to 51%, 23% and 8%.

3.26 The manufacturer submitted probabilistic and incremental cost-effectiveness estimates at the request of the Committee based on the revised model but including the effectiveness estimates resulting from the mixed-treatment comparison analysis. This analysis also included the patient access scheme. The manufacturer did not provide any modelling that assumed a constant relationship between ACR20, 50 and 70 response rates because it claimed that the certolizumab pegol clinical trial data showed no constant relationship. The manufacturer also suggested that it was unclear whether it would be appropriate to use this methodology when ACR response rate was a categorical variable.

3.27 In the incremental analysis including C87014 and the two direct comparisons, as well as the patient access scheme, certolizumab pegol plus methotrexate dominated all comparator TNF inhibitors, except etanercept plus methotrexate. For the latter the incremental QALY gain was 0.101 and incremental costs were £1481, resulting in an ICER of £14,722 per QALY gained for etanercept (that is, certolizumab pegol was less costly and less effective than etanercept). In the probabilistic sensitivity analysis, the probability of certolizumab pegol plus methotrexate being cost effective at a willingness-to-pay threshold of £20,000 per QALY gained was 48.7%. Certolizumab pegol monotherapy was less costly and less effective than etanercept monotherapy, and dominated adalimumab monotherapy. The probability of certolizumab monotherapy being cost effective at £20,000 per QALY gained was 46.2%.
3.28 Full details of all the evidence are in the manufacturer’s submission and the ERG report, which are available from www.nice.org.uk/TA186

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of certolizumab pegol, having considered evidence on the nature of rheumatoid arthritis and the value placed on the benefits of certolizumab pegol by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

4.1 The Committee was advised by the patient experts about the impact of rheumatoid arthritis on their quality of life and also heard the patient testimonials on the impact of the condition. The Committee was also advised of the difficulties of predicting which TNF inhibitor will produce the best therapeutic effect for each individual patient. Clinical specialists and patient experts emphasised the need to have a variety of biological DMARD treatments available for moderate to severe rheumatoid arthritis. The Committee also heard that certolizumab pegol may penetrate inflamed tissue better than other available TNF inhibitors. The clinical specialists pointed out that certolizumab pegol may be of benefit for people who have a lower response to other biological DMARDs. The Committee heard from clinical specialists and patient experts that published evidence and clinical practice suggest that certolizumab pegol has a rapid onset of action. Clinical specialists also stated that ideally DMARD therapy should be introduced early so that there is less joint damage and better long-term control of the condition and quality of life. The clinical specialists also pointed out that for ideal management of their condition, people should have early access to specialist centres.
4.2 The Committee discussed the decision problem in the manufacturer’s submission, noting comments from consultees during the consultation on the appraisal consultation document about the most appropriate comparators for certolizumab pegol. The Committee considered that existing NICE guidance on TNF inhibitors for the treatment of rheumatoid arthritis had been in place for a number of years and therefore it was appropriate to consider, as the manufacturer had done, certolizumab pegol in comparison with the biological DMARDs rather than conventional DMARDs.

4.3 The Committee discussed the clinical effectiveness of certolizumab pegol in people with moderate to severe active rheumatoid arthritis. The Committee agreed that there was sufficient evidence from the placebo-controlled trials of certolizumab pegol to conclude that certolizumab pegol monotherapy had greater clinical effectiveness than placebo and that certolizumab pegol in combination with methotrexate was more clinically effective than placebo plus methotrexate.

4.4 The Committee discussed the manufacturer’s four alternative mixed-treatment comparisons comparing certolizumab pegol with other biological DMARDs, which had been provided in response to a request for additional information. The Committee noted that some versions of the mixed-treatment comparison included the unpublished RCT (C87014) that the ERG had indicated should have been included, as well as two studies that made direct comparisons between etanercept and infliximab. The Committee noted that the methods used to complete the mixed-treatment comparison had not assumed a constant relationship between ACR20, 50 and 70 and that some results were irreconcilable, for example ACR20 results that were similar to or lower than ACR50 results for etanercept combination therapy. The Committee considered that the methods used by the manufacturer to complete the analysis had led to results that were not internally consistent.
4.5 The Committee considered the heterogeneity of the studies in the indirect comparison analysis and subsequently the mixed-treatment comparison, in particular the lower number of previous DMARDs, lower doses of methotrexate, shorter disease duration and the lower response rates for the placebo arms of the two RAPID studies compared with trials of some other agents. The Committee was also mindful of comments made on the appraisal consultation document about the exclusion of relevant tocilizumab studies and inclusion of adalimumab studies in which the populations may not have reflected the UK population. The Committee discussed the differing response rates in the placebo arms of the RAPID and C87014 studies. The Committee considered that the placebo arm of C87014 showed response rates that were generally consistent with other studies of TNF inhibitors, and that its exclusion could result in an overestimate of the relative effect of certolizumab pegol. However, the Committee acknowledged that the C87014 study had included a non-optimal unlicensed dose of certolizumab pegol (400 mg monthly) and therefore the results from that study may underestimate the relative effect of certolizumab pegol.

4.6 The Committee discussed the results of the mixed-treatment comparison. In doing so it was mindful of the potential limitations of the methods used (section 4.4) and the differences between the studies identified (section 4.5). It noted that in some versions of the mixed treatment comparisons, the point estimates of the effectiveness of certolizumab pegol compared with comparator treatments had been reduced compared with the original indirect comparison analysis, and that in all versions the uncertainty around the estimates of effect had increased. The Committee noted that there was a high degree of uncertainty around the effectiveness point estimates, demonstrated by the wide overlapping confidence intervals. The Committee considered that head-to-head RCTs would help clarify the differences in clinical effectiveness between the different TNF inhibitors. The Committee recognised the
heterogeneity of the studies, highlighted by the mixed-treatment comparison, as well as the potential methodological limitations and concluded that there was no convincing evidence that certolizumab pegol was more or less effective than other TNF inhibitors.

Cost effectiveness

4.7 The Committee discussed the manufacturer’s patient access scheme. The Committee considered the costs of administering the scheme and noted the manufacturer’s analysis identified that for the majority of hospitals there would be no additional cost. The Committee noted that for the remaining hospitals there would be an additional administrative burden, but considered that the manufacturer’s analyses suggested that the additional costs per patient, projected over 3 years in their analysis, were acceptable.

4.8 The Committee discussed the manufacturer’s original and revised economic models and the response to the requests for further information. The Committee noted that rituximab had been removed from the analyses as requested. The Committee discussed the manufacturer’s explanation of the differences in the utility and cost estimates between the original and revised models (see section 3.21). The Committee doubted the likelihood of the assumptions about changes in utility while on treatment with TNF inhibitors. This was because they were based on the assumption that people experienced a continual improvement in utility until they stopped treatment. The Committee considered that people may experience a reduction in utility before treatment was stopped. However, the Committee was persuaded that because the manufacturer had modelled the same assumption for all TNF inhibitors, then the estimates of incremental cost effectiveness would not be sensitive to this assumption.

4.9 The Committee discussed the sensitivity analyses provided by the manufacturer including those that changed the infusion costs of intravenously administered drugs. It noted that the original model
assumed that 92% of intravenous infusions would cost £1334, based on the tariff for day-case administration of intravenous drugs. At the request of the Committee the manufacturer had provided revised analyses using lower cost estimates (£142 and £279) than had been used in the original model. The Committee noted that using the lower costs, infliximab was no longer dominated by certolizumab pegol, and that the ICERs presented were £7000 and £3700 per QALY gained respectively. The Committee considered that although infusion cost had an effect on the ICER, in this instance it should not be a critical consideration.

4.10 The Committee discussed the cost-effectiveness estimates submitted by the manufacturer based on the mixed-treatment comparison including the three additional studies and the patient access scheme. The Committee noted that these indicated that certolizumab pegol plus methotrexate was the least costly TNF inhibitor and gave more QALYs than adalimumab and infliximab but fewer than etanercept. In addition, certolizumab pegol had the highest probability of being cost effective at £20,000 per QALY gained. The Committee noted that estimates of similar magnitude had been provided using the original and revised models before the patient access scheme had been formally accepted, and before clarification had been requested. The Committee expressed concern about the overall accuracy of the various cost-effectiveness estimates because of the uncertainty about the clinical effectiveness of certolizumab pegol compared with the other TNF inhibitors. However, the Committee was persuaded that when the patient access scheme was in place, the cost of certolizumab pegol was not out of line with the other TNF inhibitors and that certolizumab pegol was likely to be similar in clinical effectiveness and adverse event profile to the other TNF inhibitors. Therefore the Committee concluded that certolizumab pegol could be considered a cost-effective option for the treatment of rheumatoid arthritis if used in the same way as other TNF inhibitors as recommended in
'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130) and if the patient access scheme is in place.

4.11 The Committee discussed comments that TNF inhibitors could be used sequentially and that certolizumab pegol should also be considered after the failure of other TNF inhibitors. The Committee noted that at the time of discussion only rituximab (an agent that depletes B cells and is not a TNF inhibitor) was recommended by NICE for use after the failure of a TNF inhibitor. In addition, the Committee noted that only a small proportion of participants (1–4%) in the certolizumab pegol trials had received previous TNF inhibitor therapy, and that no evidence had been provided by the manufacturer for the use of certolizumab pegol after the failure of other TNF inhibitors. The Committee was therefore unable to make recommendations about the use of certolizumab pegol following failure of other TNF inhibitors. However, it considered that the recommendation for sequential TNF inhibitor use in the event of stopping treatment because of an adverse event in the first 6 months (as in NICE technology appraisal guidance 130) should also apply to certolizumab pegol.
5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/TA186).
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Research recommendations

The Committee recommended that randomised controlled trials that compare certolizumab pegol with other TNF inhibitors are carried out.

7 Related NICE guidance

Published

**Under development**

NICE is developing the following guidance (details available from www.nice.org.uk):

- Tocilizumab for the treatment of rheumatoid arthritis (publication expected May 2010)
- Golimumab for the treatment of people with rheumatoid arthritis who are methotrexate naive (publication date to be confirmed)
- Golimumab for the treatment of people with rheumatoid arthritis that has failed to respond to previous anti-rheumatic drugs (publication date to be confirmed)

### 8 Review of guidance

8.1 The guidance on this technology will be considered for review by the Guidance Executive in September 2010. The review of NICE technology appraisal guidance 130 (2007) on adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis is scheduled for consideration at this date.

Andrew Dillon
Chief Executive
February 2010
Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A  Appraisal Committee members

The Appraisal Committee is one of NICE’s standing advisory committees. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets four times a month except in December, when there are no meetings. The Committee membership is split into four branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

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

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

Dr Jane Adam (Chair)
Department of Diagnostic Radiology, St George’s Hospital

Professor Philip Home (Vice Chair)
Professor of Diabetes Medicine, Newcastle University

Professor A E Ades
MRC Senior Scientist, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol

Mrs Elizabeth Brain
Lay Member

Professor Karl Claxton
Professor of Health Economics, University of York

Dr Fiona Duncan
Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool
Mr Christopher Earl
Surgical Care Practitioner, Renal Transplant Unit, Manchester Royal Infirmary

Dr Paul Ewings
Statistician, Taunton & Somerset NHS Trust, Taunton

Professor John Geddes
Professor of Epidemiological Psychiatry, University of Oxford

Mr John Goulston
Chief Executive, Barking, Havering and Redbridge Hospitals NHS Trust

Mr Adrian Griffin
VP Strategic Affairs, LifeScan, Johnson & Johnson

Professor Jonathan Grigg
Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr Vincent Kirkbride
Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Dr Ian Lewin
Consultant Endocrinologist, North Devon District Hospital

Dr Alec Miners
Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr James Moon
Consultant Cardiologist and Senior Lecturer, University College London Hospital (UCLH) and UCL

Dr Nick Murray
Senior Lecturer and Consultant in Medical Oncology, University of Southampton

Dr Ann Richardson
Lay Member

Mrs Angela Schofield
Chairman, Bournemouth and Poole Teaching PCT

Mr Mike Spencer
General Manager, Cardiff and Vale NHS Trust – Facilities and Clinical Support Services
Professor Iain Squire  
Consultant Physician, University Hospitals of Leicester

Professor Andrew Stevens  
Professor of Public health, Department of Public Health and Epidemiology. University of Birmingham

Mr David Thomson  
Lay Member

Mr William Turner  
Consultant Urologist, Addenbrooke's Hospital

Dr Luke Twelves  
General Practitioner, Ramsey Health Centre, Cambridgeshire

Dr John Watkins  
Clinical Senior Lecturer / Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales

Dr Anthony S Wierzbicki  
Consultant in Metabolic Medicine / Chemical Pathology, Guy’s and St Thomas’ Hospitals NHS Trust

Dr Olivia Wu  
Reader in Health Economics, University of Glasgow
B  NICE project team

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

Helen Tucker
Technical Lead

Helen Chung
Technical Adviser (until October 2009)

Zoe Garrett
Technical Adviser (from October 2009)

Bijal Joshi
Project Manager
Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration:

- Connock M, et al., Certolizumab pegol (CIMZIA®) for the treatment of Rheumatoid Arthritis, August 2009

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II had the opportunity to give their expert views. Organisations listed in I and II also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- UCB Pharma

II Professional/specialist and patient/carer groups:

- British Health Professionals in Rheumatology
- British Society for Rheumatology
- National Rheumatoid Arthritis Society
- Royal College of Nursing
- Royal College of Physicians

III Other consultees:

- Department of Health
- Welsh Assembly Government
IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Abbott Laboratories
- Pfizer
- Roche Products
- Wyeth Pharmaceuticals

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on certolizumab pegol by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Clive Kelly, Consultant Rheumatologist, nominated by The British Society for Rheumatology – clinical specialist
- Dr Colin Pease, Consultant Rheumatologist, nominated by The British Society for Rheumatology – clinical specialist
- Mrs Ailsa Bosworth, Chief Executive, nominated by The National Rheumatoid Arthritis Society – patient expert
- Ms Jean Burke, Management Consultant and NRAS volunteer, nominated by The National Rheumatoid Arthritis Society – patient expert

D Representatives from the following manufacturer/sponsor attended Committee Meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- UCB Pharma