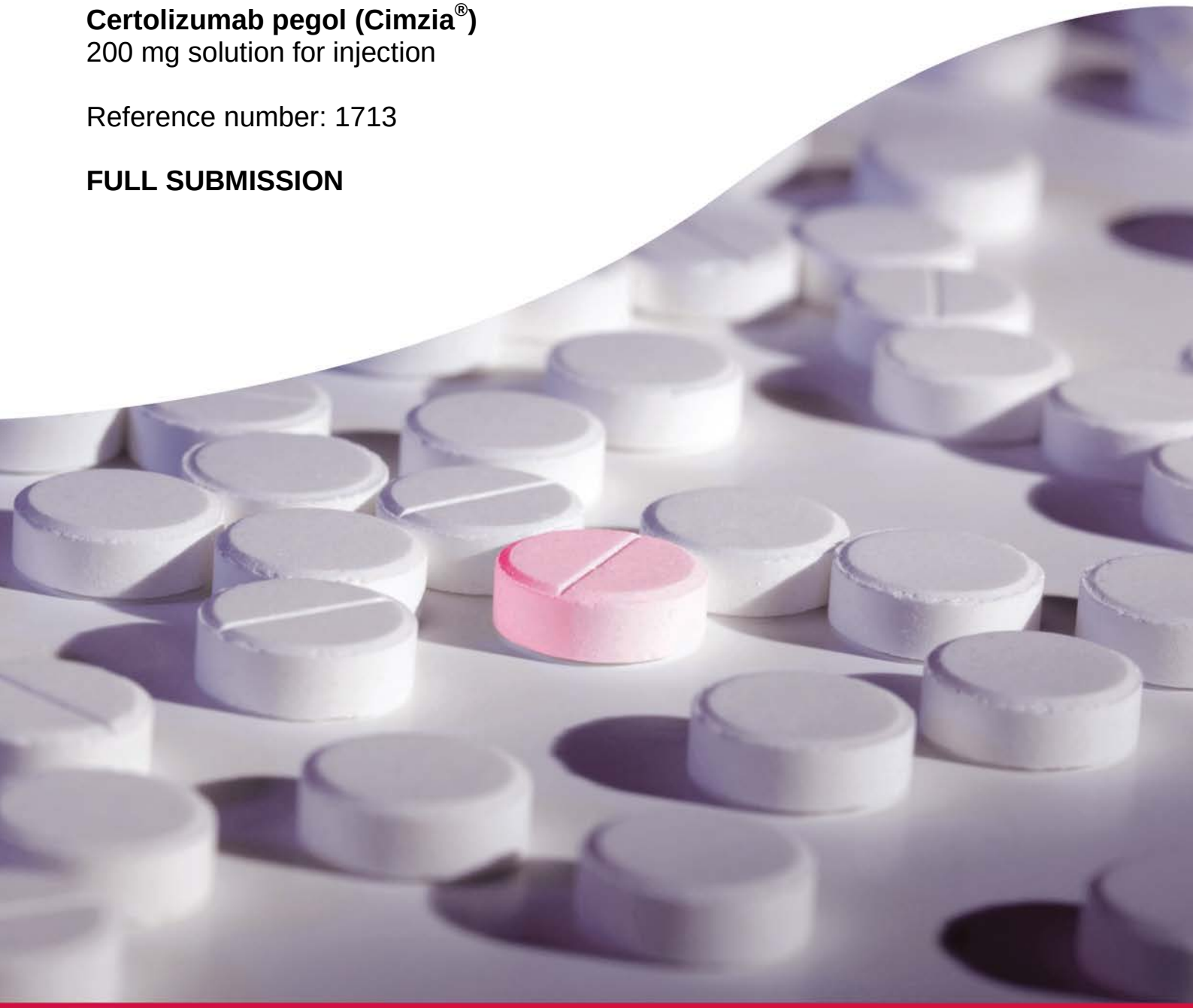
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Certolizumab pegol (Cimzia®)
200 mg solution for injection

Reference number: 1713

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Certolizumab pegol (Cimzia®) 200 mg solution for injection. Reference number: 1713. September 2014.

AWMSG Secretariat Assessment Report
Certolizumab pegol (Cimzia®) 200 mg solution for injection

This assessment report is based on evidence submitted by UCB Pharma Ltd on 22 May 2014[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Certolizumab pegol (Cimzia®), in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. Certolizumab pegol can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate[2].
Dosing	The recommended starting dose of certolizumab pegol (Cimzia®) for adult patients with psoriatic arthritis is 400 mg (two 200 mg pre-filled syringes) administered by subcutaneous injection at weeks 0, 2 and 4. The recommended maintenance dose is 200 mg every two weeks; an alternative maintenance dosing of 400 mg every four weeks can be considered once clinical response is confirmed. Methotrexate should be continued during treatment with certolizumab pegol where appropriate. Clinical response is usually achieved within 12 weeks of treatment; continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment. Refer to the Summary of Product Characteristics (SPC) for further information[2].
Marketing authorisation date	25 November 2013[3] (licensed for treatment of moderate to severe, active rheumatoid arthritis on 1 October 2009; see SPC for full licensed indication[2,4]).

2.0 DECISION CONTEXT

2.1 Background

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy[5] affecting up to one third of patients with psoriasis; in addition to psoriatic lesions, symptoms can include joint inflammation, enthesitis and dactylitis[6]. Treatment options typically include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), sulfasalazine, leflunomide and ciclosporin[5–8]. In patients refractory or intolerant to DMARDs, patients commonly receive medicines that inhibit tumour necrosis factor (TNF) alpha[5–8]. Certolizumab pegol is an inhibitor of this key pro-inflammatory cytokine[2].

The National Institute for Health and Care Excellence (NICE) recommends that TNF alpha inhibitor treatment for PsA should be considered only in patients with peripheral arthritis, with at least three tender joints and at least three swollen joints, that is refractory despite therapy with two or more standard DMARDs, alone or in

combination, using the least expensive medicine in this class[7,8]. Recommended TNF alpha inhibitors include adalimumab, etanercept, golimumab and infliximab[7–10]; ustekinumab is not recommended for use for the treatment of active PsA[11]. Treatment with a TNF alpha inhibitor should be discontinued in patients who do not demonstrate an adequate response to treatment by 12 weeks, defined as an improvement in at least two of the four Psoriatic Arthritis Response Criteria (PsARC; one of which has to be the joint tenderness or swelling score) and no worsening in any of the four criteria (see PsARC response in the Glossary). Patients whose disease has a Psoriasis Area Severity Index (PASI75) response (see Glossary) at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response[7,8].

2.2 Comparators

The comparators included in the company submission were:

- Adalimumab
- Etanercept
- Golimumab
- Infliximab
- Standard of care (SoC), consisting of treatment with conventional (synthetic) DMARDs

2.3 Guidance and related advice

- NICE. Systemic biological therapy for psoriasis and psoriatic arthritis (2014)[7].
- NICE. Technology Appraisal (TA) 313. Ustekinumab for treating active psoriatic arthritis (2014)[11].
- The British Society for Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR). The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics (2013)[5].
- European League Against Rheumatism. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies (2012)[12].
- NICE. Clinical Guideline 153. Psoriasis: the assessment and management of psoriasis (2012)[13].
- NICE. TA220. Golimumab for the treatment of psoriatic arthritis (2011)[9].
- NICE. NICE guidance on biologic drugs for the treatment of psoriatic arthritis (2011)[8].
- NICE. TA199. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (2010)[10].
- Scottish Intercollegiate Guidelines Network. SIGN Guidelines 121: Diagnosis and management of psoriasis and psoriatic arthritis in adults (2010)[14].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

As evidence of comparative clinical effectiveness, the applicant company has provided the RAPID-PsA (PsA001) study, which compared certolizumab pegol and placebo. Additionally, the company submission includes a mixed treatment comparison (MTC), comparing certolizumab pegol to adalimumab, etanercept, golimumab and infliximab[1].

3.1 RAPID-PsA study

This is an ongoing phase III, multicentre, randomised, double-blind, parallel-group, placebo-controlled study that evaluated the effectiveness of certolizumab pegol in patients (aged ≥ 18 years) with adult-onset active and progressive PsA[6,15]. The trial was comprised of five study periods:

- Screening period (up to five weeks).

- Placebo-controlled, double-blind treatment period (weeks 0–24) where patients were randomised (1:1:1) to receive either placebo or certolizumab pegol as one of two treatment regimens (400 mg certolizumab pegol at weeks 0, 2 and 4 loading doses, followed by either 200 mg certolizumab pegol every two weeks [Q2W] or 400 mg certolizumab pegol every four weeks [Q4W], administered by subcutaneous injection). Patients in the placebo group who failed to achieve a 10% improvement from baseline in both swollen and tender joints at weeks 14 and 16 were randomised (1:1) at week 16 to the two certolizumab pegol treatment groups in the dose-blind treatment period (see below)[1,6].
- Dose-blind treatment period (week 24–48); patients in the placebo group were either randomised (1:1) to receive certolizumab pegol 200 mg Q2W or 400 mg Q4W (after receiving loading doses) at week 24.
- Open-label treatment period (weeks 48–216; ongoing) where patients continue to receive the initially assigned dose.
- Safety follow-up period (weeks 216–224; to be completed)[6].

The co-primary endpoints were the proportion of American College of Rheumatology 20% (ACR20) responders at week 12 and the change from baseline in modified Total Sharp Score (mTSS) at week 24 (see Glossary for endpoint definitions)[6]. The proportion of ACR20 responders at week 12 was significantly greater in the certolizumab pegol groups; this improvement was observed regardless of prior TNF alpha inhibitor use. However, some of the predefined imputation methods led to physiologically implausible changes in mTSS, which do not accurately portray subject response, and this endpoint was therefore not met[6]. Post hoc analyses using different imputation methodology led to results that were more realistic and a statistically significant improvement was demonstrated in the combined certolizumab pegol group versus placebo[1,6]. Other key secondary endpoints supported the analysis of the ACR20 primary endpoint[6]. Furthermore, certolizumab pegol-treated patients reported significant improvement in physical function, pain, fatigue, and health-related quality-of-life measures[6]. See Table 1 for an overview of endpoints.

Table 1. Overview of endpoints from RAPID-PsA study[1,6,15,16].

	Certolizumab pegol			Placebo (n = 136)	Treatment difference: combined group versus placebo
	200 mg Q2W (n = 138)	400 mg Q4W (n = 135)	Combined (n = 273)		
Primary endpoints					
Proportion of ACR20 responders at week 12 (95% CI)	58.0% (49.7 to 66.2)	51.9% (43.4 to 60.3)	54.9% (49.0 to 60.8)	24.3% (17.1 to 31.5)	30.7% (21.4 to 40.0) p < 0.001
mTSS change from baseline at week 24 - predefined analysis†	11.5	25.1	18.3	28.9	p = 0.203
Secondary and ancillary endpoints					
Proportion of ACR20 responders at week 24 (95% CI)	63.8% (55.7 to 71.8)	56.3% (47.9 to 64.7)	60.1% (54.3 to 65.9)	23.5% (16.4 to 30.7)	36.5% (27.3 to 45.7) p < 0.001
Proportion of PASI75 responders at week 24 (95% CI)*	62.2%	60.5%	61.4%	15.1%	46.3% (35.7 to 56.9) p < 0.001
Proportion of PsARC responders at week 24	78.3%	77.0%	77.7%	33.1%	p < 0.001
mTSS change from baseline at week 24 - post hoc analysis (95% CI)†	0.01 (−0.14 to 0.15)	0.11 (−0.04 to 0.26)	0.06 (−0.06 to 0.17)	0.28 (0.13 to 0.42)	−0.22 (0.38 to −0.06) p = 0.007

ACR20: American College of Rheumatology 20%; CI: confidence interval; mTSS: modified total Sharp score; PASI75: Psoriasis Area and Severity Index 75% response; PsARC: Psoriatic Arthritis Response Criteria; Q2W: every two weeks; Q4W: every four weeks.
95% CI provided where available.
* Endpoint analysed in the subgroup of patients with psoriasis involving at least 3% body surface area. Patient numbers: 200 mg Q2W group = 90; 400 mg Q4W = 76; placebo = 86. See Glossary for further information.
† Study was not powered to detect statistical significance between individual certolizumab pegol dosage groups and placebo.

3.2 Mixed Treatment Comparison

In the absence of data comparing certolizumab pegol with other TNF alpha inhibitors for the treatment of PsA, the company submission includes a systematic review and MTC utilising Bayesian network analysis methods to evaluate the relative efficacy of these treatments[1]. The systematic review identified all randomised controlled trials (RCTs) that included treatment with a DMARD, such as a TNF alpha inhibitor, in patients with adult-onset PsA who have previously failed at least one DMARD. Studies must have reported a relevant outcome, which included ACR20, PASI75 and PsARC. Prior TNF alpha inhibitor exposure was not reported for all studies identified for analysis, and so the main analyses were conducted using only TNF alpha inhibitor-naive patients[1].

The results comparing the most relevant outcomes for certolizumab pegol versus other TNF alpha inhibitors are presented in Table 2. No statistically significant differences

were identified between the TNF alpha inhibitors for almost all outcomes, with the exception of quality-of-life as measured by the Short Form-36 (SF-36) Physical Component Summary (PCS), where statistically significant improvements were identified for adalimumab and etanercept at 24 weeks and infliximab at 12 weeks in comparison to certolizumab pegol[1].

Table 2. Overview of outcomes compared via MTC at 24 weeks[1].

Comparator	PsARC		ACR20	PASI75
	Comparator versus placebo OR (95% CrI)	Combined certolizumab pegol versus comparator OR (95% CrI)	Probability of achieving response (95% CI)	Probability of achieving response (95% CI)
Combined certolizumab pegol	¶¶	¶¶	¶¶	¶¶
Adalimumab	¶¶	¶¶	¶¶	¶¶
Etanercept	¶¶	¶¶	¶¶	¶¶
Golimumab	¶¶	¶¶	¶¶	¶¶
Infliximab	¶¶	¶¶	¶¶	¶¶
Placebo	-	¶¶	¶¶	¶¶

* Statistically significant difference.
¶¶ Commercial in confidence figures removed.
ACR20: American College of Rheumatology 20%; CI: confidence interval; CrI: credible interval; OR: odds ratio; PASI75: Psoriasis Area and Severity Index 75% response; PsARC: Psoriatic Arthritis Response Criteria.

3.3 Comparative safety

During the 24-week double-blind phase of the RAPID-PsA study, no new safety signals were identified. The incidence of treatment-emergent adverse events (TEAEs) reported during the double-blind phase was 207/332 (62.3%) in the combined certolizumab pegol group versus 92/136 (67.6%) in the placebo group[6]. In addition, the incidence of TEAEs judged to be treatment-related was comparable between these groups (86 [25.9%] and 37 [27.2%], respectively), as was the incidence of serious TEAEs (22 [6.6%] versus 6 [4.4%], respectively). All of the afore-mentioned incidences were similar between the two certolizumab pegol groups. The incidence of permanent treatment discontinuation due to TEAEs was ten (3.0%) in the combined certolizumab pegol group versus two (1.5%) in the placebo arm. There were two deaths during the double-blind phase of the study, both in patients receiving certolizumab pegol[6].

At the time of licensing, the Committee for Medicinal Products for Human Use (CHMP) noted that the safety profile for certolizumab pegol in patients with PsA was consistent with previous experience in patients with rheumatoid arthritis and was as expected for a TNF alpha inhibitor. Measures related to liver function analysis were among the most common TEAEs (alanine transaminase levels increased: 3.6% in the combined certolizumab pegol group versus 1.5% in the placebo group; aspartate transaminase increased: 3.0% versus 0.7%, respectively) and seemed to be more common in the PsA population than in rheumatoid arthritis cohorts earlier studied[6]. Hepatic events are known risks for certolizumab pegol treatment and were already addressed in the Risk Management Plan and SPC[2,6].

3.4 AWTTC critique

- During the RAPID-PsA study, the co-primary endpoint of change from baseline in mTSS using pre-defined imputation methodology did not identify a statistically significant difference between certolizumab pegol and placebo[6,15]. However, CHMP concluded that these imputation rules led to changes from baseline in mTSS that were physiologically implausible and post hoc analysis using a different imputation method led to changes that were concluded to be more realistic and identified a statistically significant difference (see Table 1)[6].
- In the absence of direct comparative evidence for certolizumab pegol versus TNF alpha inhibitors, the applicant company has provided an MTC (see Section 3.2). The applicant company acknowledges the heterogeneity of the studies included in the MTC, and the inherent limitations of this approach[1]. Conclusions drawn from the MTC should be considered in this light.
- The MTC provided by the applicant company compares certolizumab pegol with other TNF alpha inhibitors for the treatment of PsA in patients who are TNF alpha inhibitor-naive; no comparative clinical effectiveness evidence has been provided in patients that have previously received a TNF alpha inhibitor[1]. However, in the pivotal RAPID-PsA study, improvement of ACR20 response rate in certolizumab pegol-treated patients versus placebo was observed regardless of prior TNF alpha inhibitor use[15].
- NICE recommends that TNF alpha inhibitor treatment for PsA should be considered only in patients with peripheral arthritis, with at least three tender joints and at least three swollen joints, that is refractory despite therapy with two or more standard DMARDs. The mean counts for swollen and tender joints in patients enrolled in the RAPID-PsA study were substantially above the required number[6–8]; however, only 47.2% of enrolled patients had previously received two or more DMARDs[1,7,8].
- The SPCs for adalimumab, etanercept, golimumab and infliximab all state under therapeutic indications that the medicine has been shown to reduce the rate of progression of peripheral joint damage[17–25]. CHMP noted that inhibition of progression of structural damage by certolizumab pegol treatment for up to 48 weeks has not been formally established in the overall population; however, in a subset of patients at higher risk of radiographic progression inhibition of radiographic progression was maintained with certolizumab pegol treatment up to Week 48. The claim of reduced rate of progression of peripheral joint damage was removed from the therapeutic indications section of the SPC and the above results were reflected in the pharmacodynamic properties section[2,6].
- While certolizumab pegol can be administered by subcutaneous injection every two or four weeks[2], golimumab is injected once every month[21,22], adalimumab treatment is every other week[17] and etanercept can be given once or twice weekly[18–20]. Additionally, certolizumab pegol, golimumab, adalimumab and etanercept can all be self-injected using the pre-filled syringe, after proper training in the technique, if their physician determines that it is appropriate and with medical follow-up as necessary[2,17,21,22,26–28]. While infliximab maintenance treatment is only required every eight weeks, the medicine must be administered as an intravenous infusion[25]. These differences in treatment frequency and administration could impact on the preferences of patients, carers and clinicians.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a primary cost-utility analysis (CUA) of certolizumab pegol compared with other TNF alpha inhibitors (adalimumab, etanercept, golimumab and infliximab) and SoC, including non-biologic DMARDs, in the treatment of PsA[1]. The economic evidence is restricted to treatment of patients who are TNF alpha inhibitor-naive and have failed one or more non-biologic DMARDs, which represents a subgroup of the licensed population; no economic evidence has been submitted in relation to use of certolizumab pegol in patients who are TNF alpha inhibitor-experienced. No second-line TNF alpha inhibitors are permitted in the model, due to a lack of clinical trial data to inform the modelling of second-line use. The applicant company has provided a secondary cost-minimisation analysis (CMA) in the same population.

A Markov model has been developed following a similar approach to that in other economic models of PsA treatment, including a model developed by a NICE evidence review group (ERG) in its appraisal of adalimumab, etanercept and infliximab in PsA[29]. The company's model includes two phases: an initial six-month period in which response to treatment is evaluated (with a three-month period explored in a scenario analysis); and a longer follow-up period over a lifetime time horizon of analysis[1]. Response to treatment is based on PsARC and PASI75 responses; however, PsARC non-responders discontinue treatment even if they reach PASI75. Health-related quality-of-life is modelled based on mapping of Health Assessment Questionnaire-Disability Index (HAQ-DI) and PASI scores to EuroQoL Health Status Questionnaire-5 dimensions (EQ-5D) data collected in the RAPID-PsA trial of certolizumab pegol[1].

In the absence of direct comparative efficacy data for certolizumab pegol and alternative TNF alpha inhibitors, a Bayesian MTC was undertaken using published RCTs of TNF alpha inhibitors with placebo as a common comparator, identified in a systematic literature review. For certolizumab pegol, combined data from the two dose regimens in TNF alpha inhibitor-naive patients in the RAPID-PsA trial are employed (see Section 3.2). Relative PsARC and PASI responses, and HAQ-DI scores estimated using 24-week data from the TNF alpha inhibitor RCTs are used in the base case analysis to model the initial six-month response to treatment period, with 12-week data explored in the three-month initial response to treatment scenario analysis. The model excludes any placebo effect-related HAQ-DI or PASI improvements observed in the SoC arms of TNF alpha inhibitor trials, and adjusts downwards the HAQ-DI and PASI scores of TNF alpha inhibitors by a proportionate amount, based on the weighted average change in HAQ-DI for PsARC responders and non-responders across the SoC arm of the RAPID-PsA trial[1].

In the long-term phase, PsARC responders continue TNF alpha inhibitor treatment. The long-term change in HAQ-DI was assessed using 48-week data from the RAPID-PsA trial, and is applied to all TNF alpha inhibitors in the absence of longer-term HAQ-DI data from other trials. It is assumed that the HAQ-DI improvement continues after the initial response period until the end of nine months (since initiating TNF alpha inhibitor treatment) based on RAPID-PsA data, after which patients are assumed to maintain their HAQ-DI improvement until treatment discontinuation. Patients were also assumed to maintain their PASI response (PASI50/75/90) while they were treated with biologics. Patients on SoC are assumed to have a constant deterioration in HAQ-DI scores of 0.018 per three months and to maintain their baseline PASI throughout[1].

Discontinuation of TNF alpha inhibitor treatment following the initial period is assumed constant at a rate of 16.5% per annum across all TNF alpha inhibitors, based on a meta-analysis of registry data conducted for the NICE ERG model[29]. After treatment discontinuation, patients' HAQ-DI and PASI scores return to their baseline levels in the base case model, with an alternative scenario explored of rebound to the same level as would have been observed for untreated patients due to the natural history (worsening) of PsA[1].

Resource use associated with management of PsA are included using a published regression model of costs based on HAQ-DI scores, estimated from a British Society of Rheumatology Biologics Register[30]. Drug acquisition costs are based on British National Formulary (BNF) list prices, with the exception of certolizumab pegol, which has a discount on the list price, based on an agreed Wales Patient Access Scheme (WPAS). Subcutaneous TNF alpha inhibitors are assumed to be self-administered and attract administration costs for one training session; however, infliximab requires intravenous infusion and attracts the costs of clinic time with each administration. SoC costs are based on the weighted average use of different non-biologic DMARDs observed in the RAPID-PsA trial. Monitoring costs are based on recommended monitoring schedules and are reported to have been verified by expert opinion[1].

AEs are not considered in the analyses. Costs and outcomes accrued beyond one year are discounted at 3.5% per annum. For the CMA, parameter estimates for comparator TNF alpha inhibitors are set equal to those for certolizumab pegol obtained from the MTC analyses, or from the RAPID-PsA trial. One-way and probabilistic sensitivity analyses have been conducted around the base case model, and scenario analyses have tested structural assumptions[1].

4.1.2 Results

The company has reported results of the base case CUA based on 24-week data/6-month initial assessment period, and a scenario analysis using 12-week data/3-month initial assessment period, as individual pair-wise comparisons of each TNF alpha inhibitor compared with SoC, and individual comparisons of certolizumab compared with TNF alpha inhibitors, as presented in Table 3.

In the context of the agreed WPAS, when response to treatment is assumed to be assessed at 24 weeks, the incremental cost per quality-adjusted life-year (QALY) gained for each of the TNF alpha inhibitors except infliximab is similar when compared against SoC. Compared against alternative TNF alpha inhibitors , certolizumab pegol is estimated to be marginally more effective and less costly than adalimumab, golimumab and infliximab, and is estimated to be less costly and marginally less effective than etanercept.

In the scenario analysis, when response to treatment is assumed to be assessed at 12 weeks, certolizumab pegol is estimated to be the least effective and least costly of the TNF alpha inhibitors.

Table 3. Results of base case CUA using 24-week data and scenario analysis using 12-week data[1].

	CZP	ETA	IFX	ADA	GOL	SoC	Plausibility issues?
Base case: 24-week initial assessment period and 24-week data from MTC analyses							
Total costs	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	Assumes initial response to treatment assessed at 24 weeks, rather than 12 weeks as suggested in the CZP SPC[2] and in clinical guidelines, and in the NICE ERG base case model.
Total QALYs	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	
ICER: TNF alpha inhibitor versus SoC	¶¶	¶¶	¶¶	¶¶	¶¶	-	
ICER: CZP versus TNF alpha inhibitor	-	¶¶	¶¶	¶¶	¶¶	-	
Scenario analysis: 12-week initial assessment period and 12-week data from MTC analyses							
Total costs	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	May be more aligned with expected initial assessment in practice; indicates that CZP is less effective and less costly than all the alternative TNF alpha inhibitors. The 24 week data in the base case model is more favourable to CZP.
Total QALYs	¶¶	¶¶	¶¶	¶¶	¶¶	¶¶	
ICER: TNF alpha inhibitor versus SoC	¶¶	¶¶	¶¶	¶¶	¶¶	-	
ICER: CZP versus TNF alpha inhibitor	-	¶¶	¶¶	¶¶	¶¶	-	

¶¶ Commercial in confidence figures removed.

ADA: adalimumab; CZP: certolizumab pegol; ETA: etanercept; ERG: Evidence Review Group; GOL: golimumab; ICER: incremental cost-effectiveness ratio (cost/QALY gained); IFX: infliximab; NICE: National Institute for Health and Care Excellence; QALY: quality-adjusted life year; SoC: standard of care; SPC: Summary of Product Characteristics; TNF: tumour necrosis factor.

In the probabilistic sensitivity analyses, all the TNF alpha inhibitors except infliximab had similar probabilities of being cost effective at a willingness to pay threshold of £20,000 per QALY gained compared with SoC; certolizumab pegol had numerically the highest probability (22.2% and 18.6% at 24- and 12-week initial assessment points, respectively). A wide range of deterministic sensitivity/scenario analyses was also conducted around the base case model. The base case results were not materially influenced by assumed baseline characteristics of patients, including their baseline HAQ-DI or PASI scores. Removal of the adjustment for placebo effects and the assumed continued improvement in HAQ-DI after initial response assessment, permitting treatment continuation based on PASI75 in PsARC non-responders, and the adoption of HAQ-DI and psoriasis-related costs as per the NICE ERG model made little difference to the base case model results. Use of the NICE ERG utility values regression model reduced the ICER for certolizumab pegol versus SoC to around £16,000 per QALY gained, reduction of the time horizon of analysis to ten years increased the ICER for certolizumab pegol versus SoC to £49,000 per QALY gained, and assuming that HAQ-DI scores rebound to the natural history score rather than to baseline score upon treatment discontinuation increased the ICER versus SoC to £45,000 per QALY gained, while certolizumab pegol remained less costly and less effective than etanercept.

Based on the Bayesian MTC, the credible intervals around mean treatment effects for each TNF alpha inhibitor for the majority of outcomes overlapped, which the company considers is demonstration of no statistically significant difference in treatment effects between certolizumab pegol and comparator TNF alpha inhibitors[1]. In the context of the WPAS, if it is assumed that certolizumab pegol and the other TNF alpha inhibitors are all therapeutically equivalent, then the CMA indicates that certolizumab pegol is the least costly TNF alpha inhibitor, irrespective of the assumed initial response to treatment period adopted in the model.

4.1.3 AWTTC critique

The base case model assumes initial response to treatment at 24 weeks, rather than 12 weeks as recommended by existing NICE guidance on TNF alpha inhibitors in PsA and suggested in the SPC for certolizumab pegol. When initial response to treatment is assessed at 12 weeks, certolizumab pegol is estimated to be the least costly and the least effective of the TNF alpha inhibitors, and the modelled differences in QALY gains would appear to challenge the assumption of therapeutic equivalence required for CMA. However, as there are no direct comparative trials of TNF alpha inhibitors, all analyses rely on MTC analyses, which are subject to limitations.

Key strengths of the economic evidence include:

- In the absence of direct comparative trial data for the TNF alpha inhibitors, the company has conducted adjusted, MTC analyses of trial data identified via a systematic literature review.
- The modelling methods adopted are broadly aligned with previous accepted approaches, and a wide range of sensitivity/scenario analyses have been conducted to explore structural and parameter uncertainty.

Key limitations and uncertainties of the economic evidence include:

- There are no direct comparative data for certolizumab pegol and alternative TNF alpha inhibitors. MTC analyses have been necessary, and the company has highlighted heterogeneity among the included trials due to differences in patient populations, treatment schedules and timing of endpoint assessments that may have influenced the results. The company notes that credible intervals around outcome estimates are overlapping in nearly all the MTC analyses, and suggests this is evidence of comparable efficacy of the TNF alpha inhibitors[1]; however, these credible intervals are wide.
- The base case analysis assumes a 24-week initial assessment of response period and uses 24-week data from the trials in the MTC analyses; however, the SPC for certolizumab pegol[2] (and other TNF alpha inhibitors[17,21,22]) notes that clinical response is usually achieved within 12 weeks of treatment, and continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment. The current NICE Technology Appraisal guidance for adalimumab, etanercept, infliximab and golimumab also states treatment should be discontinued in people whose PsA has not shown an adequate response using PsARC at 12 weeks[9,10]. The scenario analysis assuming a 12-week initial response to treatment and using 12-week data from the MTC may therefore be more appropriate than the base case analysis.
- When initial response to treatment is at 12 weeks, certolizumab pegol is estimated to be the least costly and the least effective of the TNF alpha inhibitors considered in the model. The modelled differences in QALY gains between certolizumab pegol and alternative TNF alpha inhibitors are more pronounced than was observed in the base case model, which would challenge the assumptions of therapeutic equivalence required for the CMA approach. The sensitivity and scenario analyses conducted for the model using a 12-week

initial response to treatment period are more limited than were conducted for the base case model.

- The economic evidence is limited to first-line use of only one TNF alpha inhibitor. The RAPID-PsA trial specifically excluded patients who had experienced primary failure to prior TNF alpha inhibitor and the economic model excludes data from TNF alpha inhibitor-experienced patients. As in the NICE ERG model, no subsequent biologic treatments have been modelled following treatment failure due to lack of robust trial data.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published cost-effectiveness analyses of certolizumab pegol use in PsA of relevance to the UK.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

A wide range of prevalence and incidence estimates for PsA are available in the literature. The company assumes a prevalence of PsA in Wales of 650 per 100,000 population, based on an estimate in a NICE commissioning guide for England[31], and an incidence of 7.2 per 100,000 population/year, as an approximate midpoint of the estimates in the literature[1]. Based on a published standardised mortality ratio of 1.36 for patients with PsA, UK life tables and the age and gender distribution of patients enrolled in the RAPID-PsA trial, the company estimates a mortality rate of 0.67% per year[1]. Applied to the Welsh population, and assuming no population growth over the next five years, this equates to a net number of patients with PsA in each year of 20,067. The NICE commissioning guide estimates that 2.4% of PsA patients receive biologic treatment[31], which applied to Wales would equate to 482 patients receiving biologic treatment per year[1].

The company anticipates uptake rates for year one, rising to year five, with most of that drawn from patients who would currently receive certain medicines [commercial in confidence data removed]. Treatment costs in the model include drug acquisition costs, with the first 10 syringes of certolizumab pegol being provided free of charge to the NHS as agreed in a WPAS. A mean patient weight of 84.43kg is assumed based on the RAPID-PsA trial. Administration costs are assumed only for infliximab, as this is the only agent that requires intravenous administration. For simplicity, it is assumed that the proportion of patients that discontinue certolizumab pegol (16.5% per year as per the economic model) is replaced by the same number of new patients commencing certolizumab pegol, and during the maintenance phase all patients are assumed to administer certolizumab pegol at a dose of 200 mg every two weeks, rather than once every four weeks[1].

5.1.2 Results

Table 4 presents the base case net uptake and cost estimates provided by the company. The introduction of certolizumab pegol is estimated to bring cost savings compared with current use of TNF alpha inhibitors, in the context of the agreed WPAS.

Table 4. Company base case budget impact estimates.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	¶¶	¶¶	¶¶	¶¶	¶¶
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients treated with certolizumab pegol each year	¶¶	¶¶	¶¶	¶¶	¶¶
Overall net cost of certolizumab pegol versus current TNF alpha inhibitors	−£62,340	−£80,167	−£111,000	−£99,009	−£89,611
¶¶ Commercial in confidence figures removed.					

An alternative estimate of PsA prevalence is explored in a sensitivity analysis. Using a lower prevalence of 0.19%, as reported in a UK-based epidemiological study[32], the number of patients eligible for certolizumab pegol treatment and the estimated cost savings are reduced, as would be predicted (Table 5).

Table 5. Company budget impact scenario analysis.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	¶¶	¶¶	¶¶	¶¶	¶¶
Uptake (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients treated with certolizumab pegol each year	¶¶	¶¶	¶¶	¶¶	¶¶
Overall net cost of certolizumab pegol versus current TNF alpha inhibitors	−£18,611	−£23,933	−£33,138	−£29,558	−£26,753
¶¶ Commercial in confidence figures removed.					

5.1.3 AWTTC critique

- There appears to be a range of PsA prevalence and incidence estimates available in the literature, which introduces uncertainty into the estimation of eligible patient numbers.
- To account for the loading dose requirements with certolizumab pegol, the company has adopted a pragmatic approach to estimate likely costs in each year.
- It is implicitly assumed that certolizumab pegol is therapeutically equivalent to the displaced TNF alpha inhibitors in this analysis, which, as noted in Section 4, is unclear.
- Collectively, the likely budget impact of use of certolizumab pegol is subject to uncertainty; however, in the context of the WPAS, and assuming therapeutic equivalence, certolizumab pegol would be less costly than alternative TNF alpha inhibitors at list prices.

5.2 Comparative unit costs

Example comparative annual costs of the first year of treatment with certolizumab pegol and alternative TNF alpha inhibitors are provided in Table 6, based on BNF list prices[32]. These costs do not include the costs of concomitant non-biologic DMARDs, or account for the agreed WPAS for certolizumab pegol (the first 10 syringes of certolizumab pegol being provided free of charge to the NHS), or any locally-agreed procurement discounts on any TNF alpha inhibitors.

Table 6. Example annual costs of certolizumab pegol and alternative TNF alpha inhibitors in PsA.

Drug	Example regimen	Annual cost*
Certolizumab pegol (Cimzia®) 200 mg prefilled syringe	400 mg at 0, 2, and 4 weeks, followed by 400 mg every 4 weeks	£10,010† in the first year, £9,295 in subsequent year
Adalimumab (Humira®) 40 mg prefilled pen	40 mg every 2 weeks	£9,156
Etanercept (Enbrel®) 50 mg prefilled pen	50 mg weekly	£9,295
Golimumab (Simponi®) 50 mg prefilled pen	50 mg monthly on the same day each month	£9,156
Infliximab (Remicade®) 100 mg vial for intravenous infusion	5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks	£13,428 in first year, £11,749 in subsequent year

* Based on BNF list prices[32], excluding any concomitant DMARDs and administration costs. Assumes 80 kg adult and no discontinuations or wastage.
† First-year cost of certolizumab pegol under the WPAS is £6,435
This table does not imply therapeutic equivalence of drugs or doses.
See relevant Summaries of Product Characteristics for full dosing details[2,17–22,25].

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, certolizumab pegol (Cimzia®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipate that certolizumab pegol (Cimzia®) may be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission highlighted that evidence from the ongoing Rapid-PsA study is likely to be available within 6–12 months[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 5 June 2014
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

American College of Rheumatology 20% (ACR20) response
ACR20 responders are those subjects with at least 20% improvement from baseline for tender joint count, swollen joint count, and at least three of the five remaining core set measures:

- Health Assessment Questionnaire-Disability Index (HAQ-DI)
- C-reactive protein (CRP)
- Patient's assessment of arthritis pain-visual analog scale (PAAP-VAS)
- Patient's global assessment of disease activity-visual analog scale (PtGADA-VAS)
- Physician's global assessment of disease activity-visual analog scale (PhGADA-VAS)[33].

Modified Total Sharp Score (mTSS) change from baseline
This was defined in the RAPID-PsA study as the change from baseline in Van der Heijde mTSS, modified for PsA by addition of hand distal interphalangeal joints[6,15]. It is a method for assessing the degree of joint damage by quantifying the extent of bone erosions and joint space narrowing for 64 and 52 joints, respectively, with higher scores representing greater damage:

- mTSS bone erosions range: 0 (best possible outcome) to 320 (worst possible outcome)
- mTSS joint space narrowing range: 0 (best possible outcome) to 208 (worst possible outcome)
- Total score range: 0 (best possible outcome) to 528 (worst possible outcome)[33].

Psoriasis Area Severity Index (PASI75) response
This was defined in the RAPID-PsA study as the proportion of patients demonstrating at least 75% improvement in the PASI score from baseline by week 24 in the subgroup of patients with psoriasis involving at least 3% body surface area. The PASI score is a measure of the average redness, thickness, and scaliness of the psoriatic skin lesions (each graded on a 0–4 scale), weighted by the area of involvement[33].

Psoriatic Arthritis Response Criteria (PsARC) response
This response is defined as improvement in two of the following factors, with at least one being an improvement in tender or swollen joint count:

- ≥ 20% improvement in physician global assessment of disease activity
- ≥ 20% improvement in patient global assessment of disease activity
- ≥ 30% improvement in tender joint count
- ≥ 30% improvement in swollen joint count.

No worsening in any PsARC component should be observed[34].

REFERENCES

1 UCB Pharma Ltd. Form B: Detailed appraisal submission. Certolizumab pegol (Cimzia®). May 2014.

2 UCB Pharma Ltd. Cimzia® 200 mg solution for injection. Summary of Product Characteristics. May 2014. Available at: http://www.medicines.org.uk/emc/medicine/22323/SPC/Cimzia+200+mg+solution+for+injection/. Accessed Jun 2014.

3 European Medicines Agency. Cimzia®. Procedural steps taken and scientific information after the authorisation. Jan 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/001037/WC500069736.pdf. Accessed Jun 2014.

4 European Medicines Agency. Assessment Report for Cimzia®. Procedure No.: EMEA/H/C/001037. Oct 2009. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001037/WC500069735.pdf. Accessed Jun 2014.

5 Coates LC, Tillett W, Chandler D et al. The 2012 BSR and BHPR guideline for the treatment of psoriatic arthritis with biologics. *Rheumatology* 2013; 52 (10): 1754-7.

6 European Medicines Agency. Assessment report: Cimzia®. Procedure No.: EMEA/H/C/001037/II/27. Jan 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001037/WC500159001.pdf. Accessed Jun 2014.

7 National Institute for Health and Care Excellence. Systemic biological therapy for psoriasis and psoriatic arthritis. May 2014. Available at: http://pathways.nice.org.uk/pathways/psoriasis#path=view%3A/pathways/psoriasis/systemic-biological-therapy-for-psoriasis-and-psoriatic-arthritis.xml. Accessed Jun 2014.

8 National Institute for Health and Care Excellence. NICE guidance on biologic drugs for the treatment of psoriatic arthritis. Apr 2011. Available at: http://www.nice.org.uk/proxy/?sourceUrl=http%3a%2f%2fwww.nice.org.uk%2fmedia%2f9BB%2f25%2fPsoriaticArthritisAlgorithm.pdf. Accessed Jun 2014.

9 National Institute for Health and Care Excellence. Technology Appraisal 220. Golimumab for the treatment of psoriatic arthritis. Apr 2011. Available at: http://guidance.nice.org.uk/TA220. Accessed Jun 2014.

10 National Institute for Health and Care Excellence. Technology Appraisal 199. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis. Aug 2010. Available at: http://guidance.nice.org.uk/TA199. Accessed Jun 2014.

11 National Institute for Health and Care Excellence. Technology Appraisal 313. Ustekinumab for treating active psoriatic arthritis. May 2014. Available at: http://guidance.nice.org.uk/TA313. Accessed Jun 2014.

12 Gossec L, Smolen JS, Gaujoux-Viala C et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis* 2012; 71 (1): 4-12.

13 National Institute for Health and Care Excellence. Clinical Guideline 153. Psoriasis: the assessment and management of psoriasis. Oct 2012. Available at: http://guidance.nice.org.uk/CG153. Accessed Jun 2014.

14 Scottish Intercollegiate Guidelines Network. SIGN Guidelines 121: Diagnosis and management of psoriasis and psoriatic arthritis in adults. Oct 2010. Available at: http://www.sign.ac.uk/guidelines/fulltext/121/index.html. Accessed Jun 2014.

15 Mease PJ, Fleischmann R, Deodhar AA et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014; 73 (1): 48-55.
16 van der Heijde D., Fleischmann R, Wollenhaupt J et al. Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: results of the RAPID-PsA 24-week phase III double-blind randomised placebo-controlled study of certolizumab pegol. *Ann Rheum Dis* 2014; 73 (1): 233-7.
17 AbbVie Ltd. Humira® 40 mg solution for injection and 40 mg/0.8 ml solution for injection. Summary of Product Characteristics. May 2014. Available at: http://www.medicines.org.uk/emc/medicine/21201/SPC/Humira+Pre-filled+Pen%2c+Pre-filled+Syringe+and+Vial/. Accessed Jun 2014.
18 Pfizer Ltd. Enbrel® 25 mg powder and solvent for solution for injection. Summary of Product Characteristics. Oct 2013. Available at: http://www.medicines.org.uk/emc/medicine/3343/SPC/Enbrel+25+mg+powder+and+solvent+for+solution+for+injection/. Accessed Jun 2014.
19 Pfizer Ltd. Enbrel® 25 mg solution for injection. Summary of Product Characteristics. Jan 2014. Available at: http://www.medicines.org.uk/emc/medicine/19161/SPC/Enbrel+25mg+solution+for+injection+in+pre-filled+syringe/. Accessed Jun 2014.
20 Pfizer Ltd. Enbrel® 50 mg solution for injection. Summary of Product Characteristics. Jan 2014. Available at: http://www.medicines.org.uk/emc/medicine/22143/SPC/Enbrel+50+mg+solution+for+injection+in+pre-filled+pen/. Accessed Jun 2014.
21 Merck Sharp & Dohme Ltd. Simponi® 100 mg solution for injection. Summary of Product Characteristics. Oct 2013. Available at: http://www.medicines.org.uk/emc/medicine/28316/SPC/Simponi+100+mg+solution+for+injection/. Accessed Jun 2014.
22 Merck Sharp & Dohme Ltd. Simponi® 50 mg solution for injection. Summary of Product Characteristics. Oct 2013. Available at: http://www.medicines.org.uk/emc/medicine/23766/SPC/Simponi+50+mg+solution+for+injection/. Accessed Jun 2014.
23 Celltrion Healthcare Co Ltd. Remsima® 100 mg powder for concentrate for solution for infusion. Summary of Product Characteristics. Jun 2014. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002576/WC500150871.pdf. Accessed Jul 2014.
24 Hospira UK Ltd. Inflectra® 100 mg powder for concentrate for solution for infusion. Summary of Product Characteristics. Sep 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002778/WC500151489.pdf. Accessed Jul 2014.
25 Merck Sharp & Dohme Ltd. Remicade® 100 mg powder for concentrate for solution for infusion. Summary of Product Characteristics. Aug 2013. Available at: http://www.medicines.org.uk/emc/medicine/3236/SPC/Remicade+100mg+powder+for+concentrate+for+solution+for+infusion/. Accessed Jun 2014.
26 Pfizer Ltd. Enbrel® 25 mg powder and solvent for solution for injection. Patient Information Leaflet. Jun 2014. Available at: http://www.medicines.org.uk/emc/medicine/14412/PIL/Enbrel+25+mg+powder+and+solvent+for+solution+for+injection/. Accessed Jun 2014.
27 Pfizer Ltd. Enbrel® 50 mg solution for injection. Patient Information Leaflet. Jun 2014. Available at: http://www.medicines.org.uk/emc/medicine/22141/PIL/Enbrel+50+mg+solution+for+injection+in+pre-filled+pen/. Accessed Jun 2014.

28 Pfizer Ltd. Enbrel® 25 mg solution for injection. Patient Information Leaflet. Jun 2014. Available at: http://www.medicines.org.uk/emc/medicine/19055/PIL/Enbrel+25mg+solution+for+injection+in+pre-filled+syringe/. Accessed Jun 2014.
29 Rodgers M, Epstein D, Bojke L et al. Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2011; 15 (10): i-329.
30 Poole CD, Lebmeier M, Ara R et al. Estimation of health care costs as a function of disease severity in people with psoriatic arthritis in the UK. *Rheumatology* 2010; 49 (10): 1949-56.
31 National Institute for Health and Care Excellence. Biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology. Jun 2013. Available at: http://www.nice.org.uk/resource/CG153/html/p/biologic-drugs-for-the-treatment-of-inflammatory-disease-in-rheumatology-dermatology-and-gastroenterology. Accessed Jul 2014.
32 British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. Apr 2014. Available at: http://www.bnf.org/bnf/index.htm. Accessed Apr 2014.
33 UCB Pharma Ltd. NCT01087788: Phase 3, multicenter, randomized, double-blind, parallel group, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in subjects with adult-onset active and progressive psoriatic arthritis (PsA). Feb 2014. Available at: http://www.clinicaltrials.gov/ct2/show/NCT01087788. Accessed Jun 2014.
34 Gottlieb A, Korman NJ, Gordon KB et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol* 2008; 58 (5): 851-64.