Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House (8th floor) 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman Professor Kenneth R Paterson
NHS SCOTLAND

Resubmission:

certolizumab pegol, 200 mg/mL solution for injection (prefilled syringe) (Cimzia®) SMC No. (590/09)

UCB Pharma Ltd

10 September 2010

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

certolizumab pegol (Cimzia®) is accepted for use within NHS Scotland.

Indication under review:

- in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adult patients when the response to disease modifying anti-rheumatic drugs, including methotrexate, has been inadequate.
- monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

In patients who continued to receive methotrexate despite an incomplete response, the addition of certolizumab pegol for 24 weeks produced a rapid and sustained reduction in the signs and symptoms of rheumatoid arthritis, inhibited structural joint damage progression and improved physical function compared with placebo.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of certolizumab pegol. This SMC advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland.

Overleaf is the detailed advice on this product.

Vice Chairman
Scottish Medicines Consortium

Indication

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 disease modifying anti-rheumatic drugs (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. It has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

Dosing Information

Initially 400mg at weeks 0, 2 and 4, followed by a maintenance dose of 200mg every 2 weeks by subcutaneous injection.

Certolizumab pegol treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis. Patients should be given the special alert card.

Available data suggest that 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.

After proper training in injection technique, patients may self-inject with certolizumab pegol if their physician determines that it is appropriate and with medical follow-up as necessary.

Product availability date

26 October 2009

Summary of evidence on comparative efficacy

Certolizumab pegol is a tumour necrosis factor alpha (TNF-α) inhibitor consisting of a recombinant humanised antibody Fab fragment conjugated to polyethylene glycol (PEG).

Evidence to support efficacy is from two pivotal studies that compared two dosage regimens of certolizumab pegol with placebo in patients already receiving a stable dose of methotrexate.

Two randomised, double-blind studies recruited adults who, despite treatment with methotrexate, had active rheumatoid arthritis according to American College of Rheumatology (ACR) criteria for ≥6 months but <15 years prior to screening. Active disease was defined as ≥9 tender and 9 swollen joints at screening and baseline, with either an erythrocyte sedimentation rate (ESR) ≥30mm/hour or a C-reactive protein (CRP) level >15 mg/litre. Patients were required to have received methotrexate for ≥6 months, with a stable dosage of ≥10 mg/week for ≥2 months prior to baseline.

Patients (n=982 in first study and n=619 in second study) were randomised 2:2:1 to receive subcutaneous injections of certolizumab pegol 400mg at weeks 0, 2, and 4, followed by 200mg or 400mg every 2 weeks thereafter, or placebo. All patients continued methotrexate at pre-study dosage. The duration of treatment was 52 and 24 weeks in the first and second study, respectively. Patients who failed to achieve a response according to ACR criteria for 20% improvement (ACR20) at weeks 12 and 14 were designated treatment failures and were withdrawn from the study at week 16. These withdrawal rates in the first study were 21%, 17% and 63% in the certolizumab pegol 200mg, 400mg and placebo groups, respectively and in the second study were 21%, 21% and 81%, respectively. Patients withdrawn at 16 weeks were offered treatment with open-label certolizumab pegol.

The primary endpoint in both studies was ACR20 response rate, defined as a decrease of ≥20% from baseline in the number of tender and swollen joints, plus a 20% improvement in at least three of the following outcomes: patient's and physician's global assessment of disease activity, patient's assessment of arthritis pain, Health Assessment Questionnaire-Disability Index (HAQ-DI), and serum CRP or ESR at week 24. A co-primary endpoint in the first study was the mean change from baseline at week 52 in the modified total Sharp score (mTSS) which quantifies the extent of bone erosions and joint space narrowing for 44 and 42 joints, respectively, with higher scores representing greater damage. In both studies analyses were based on the intent-to-treat (ITT) populations, which consisted of all randomised patients.

In both studies the ACR20 response rate at week 24 was significantly higher in the certolizumab pegol groups compared with placebo. The responder rates in the certolizumab pegol 200mg, 400mg and placebo groups in the first study were 59%, 61% and 14%, respectively and in the second study were 57%, 58% and 8.7%, respectively. In both studies differences from placebo were significant at week 1 and sustained throughout the study. Certolizumab pegol significantly inhibited the progression of structural joint damage compared with placebo at 52 weeks (co-primary outcome in first study) with a change in mTSS from baseline of 0.4, 0.2 and 2.8 units in the certolizumab pegol 200mg, 400mg and placebo groups, respectively. Differences between the certolizumab pegol and placebo groups were also significant at 24 weeks in both studies. Certolizumab pegol was superior to placebo in ACR50 and ACR70 response rates. In the 52-week study ACR50 response rates were 38%, 40% and 7.6% and ACR70 response rates were 21%, 23% and 3.5% for the certolizumab 200mg, 400mg and placebo groups, respectively. In the 24-week study ACR50 response rates were 32%, 33% and 3.1% and ACR70 response rates were 16%, 11% and 0.8% for the certolizumab 200mg, 400mg and placebo groups, respectively. There was also significant improvement in all ACR core components, including reductions in swollen and tender joint count, which were evident at week 1 and sustained until end of study. The 28 joint disease activity score (DAS28 (ESR)) calculated using the tender and swollen joint count (carried out on 28 joints), the ESR (mm/hour) and the Patient's Global Assessment of Disease Activity, was a secondary endpoint in both studies. Compared with placebo, certolizumab pegol significantly improved the DAS28 (ESR) and also produced a clinically significant improvement in the HAQ-DI which measures physical function from week one (week 2 for second study) until end of study. Significantly more patients in the certolizumab pegol groups achieved clinically meaningful improvements compared with placebo in health-related quality of life (HRQoL), as measured by the Short Form (SF-36) Health Survey physical and mental component scores.

The 24-week study was completed by 355 of 619 patients and 96% (342/355) of the completers entered an open-label extension study. Using non-responder imputation, ACR50 response rates were 47%, 45% and 39% and ACR70 response rates were 19%, 23% and 20% at 24, 100 and 148 weeks respectively. Mean change from baseline in mTSS using linear extrapolation was 0.61, 0.58 and 0.75 at 24, 100 and 148 weeks respectively.

A randomised, double-blind, placebo-controlled study of certolizumab pegol as monotherapy employed an unlicensed dose regimen. The inclusion criteria were similar to the combination studies previously described except that patients had failed ≥1 prior DMARD due to lack of efficacy or to intolerance. Two hundred and twenty patients were randomised 1:1 to receive subcutaneous certolizumab pegol 400mg or placebo every 4 weeks for 24 weeks. The primary endpoint of ACR20 response at week 24 was significantly greater for the certolizumab pegol group compared with the placebo group, 45% and 9.3%, respectively. Differences were significant at week one and sustained throughout the study. Significant improvements in ACR50, ACR70, ACR components, DAS28 (ESR)-3 and all patient-reported outcomes were also observed early with certolizumab pegol and sustained throughout the study.

Summary of evidence on comparative safety

There is no comparative safety evidence for certolizumab pegol in rheumatoid arthritis. In the placebo-controlled studies previously described, most adverse events (AEs) were mild or moderate in intensity. Infections were the most frequent AEs in both certolizumab pegol and placebo groups. Other common AEs in patients treated with certolizumab pegol were headache, hypertension and back pain.

Serious infections, including sepsis and tuberculosis (including miliary, disseminated and extrapulmonary disease), and opportunistic infections (e.g. histoplasmosis, nocardia, candidiasis) have been reported in patients receiving certolizumab pegol. Some of these events have been fatal. Reactivation of hepatitis B virus has occurred in patients who are chronic carriers of this virus receiving TNF antagonists. Some cases have had a fatal outcome.

The summary of product characteristics (SPC) for certolizumab pegol notes that patients with rheumatoid arthritis may not manifest typical symptoms of infection, including fever, due to their disease and concomitant medicinal products. Therefore, early detection of any infection, particularly atypical clinical presentations of a serious infection, is critical to minimise delays in diagnosis and initiation of treatment. Patients must be monitored closely for signs and symptoms of infections including tuberculosis before, during and after treatment with certolizumab pegol, and as its elimination may take up to 5 months, monitoring should be continued throughout this period.

The observed incidence rate of malignancies in the RA clinical studies of certolizumab pegol (all doses) was estimated at 725/100,000 person-years compared with a mean incidence of malignancies in the general population of 595/100,000.

Anti–certolizumab pegol antibodies were detected in 6.4% and 5.1% of patients receiving certolizumab pegol in the 52-week and 24-week studies, respectively. The SPC notes that a pharmacodynamic model based on the phase III study data predicts that around 15% of patients develop antibodies in 6 months at the recommended dose regimen without methotrexate co-treatment. This number decreases with increasing doses of concomitant methotrexate treatment. These data are reasonably in agreement with observed data.

Injection site pain was observed in 1.5% of patients and no cases led to withdrawal.

Long term safety data are limited.

Summary of clinical effectiveness issues

Certolizumab pegol has demonstrated significantly improved outcomes in ACR response rate and mTSS compared with placebo but it has not been directly compared with other drugs in patients with rheumatoid arthritis. A Bayesian mixed treatment comparison (MTC) was presented in the submission and included twenty studies of biological DMARDs, (certolizumab pegol, adalimumab, infliximab, etanercept, tocilizumab and rituximab). There were fifteen combination studies (with methotrexate) and five monotherapy studies. The common comparator was placebo (monotherapy) or placebo plus methotrexate (combination therapy) in all studies except two that compared infliximab and etanercept. The monotherapy comparison included certolizumab pegol administered by an unlicensed dose regimen (400mg every four weeks). The MTC credible intervals were wide. Limitations of the MTC included substantial variation in study duration, patient numbers, concomitant medications and methotrexate dose. The MTC excluded a study of certolizumab pegol in combination with methotrexate versus methotrexate alone that was considered by the European Medicines Agency to be one of four main studies although it used an unlicensed dose regimen. However SMC was satisfied that the MTC conclusion, that certolizumab pegol is at least as effective as adalimumab, etanercept and infliximab, was reasonable.

The population in the pivotal studies included patients with moderate to severe rheumatoid arthritis, however in practice tumour necrosis factor alpha inhibitors are generally reserved for patients with more severe disease i.e., DAS28 >5.1 who have had trials of two DMARDs including methotrexate (unless contraindicated).

Three-year data from the open label extension of the 24-week study suggests that adding certolizumab pegol to methotrexate in patients with active rheumatoid arthritis produces sustained clinical improvement, inhibits joint damage progression and is well tolerated.

Available data suggest that clinical response with certolizumab pegol was usually achieved within 12 weeks of treatment, thereby allowing the decision to continue or withdraw treatment to be made at this time. Available SPC data for infliximab suggest that its clinical response is also usually achieved within 12 weeks of treatment. It is unsubstantiated if this response time is shorter than other comparators. Existing guidance recommends a trial of 6 months prior to assessing response to TNF-α inhibitors.

The conjugation of certolizumab with PEG extends its half-life allowing administration (subcutaneously) every two weeks. Self-administration after adequate training may be possible for some patients. This administration route and dosage interval may have benefits for both patients and the service. Comparators that are administered subcutaneously are adalimumab (every two weeks) and etanercept (once or twice weekly), both of which may also be self-administered. Comparators that are administered by intravenous infusion are infliximab (every eight weeks after initial loading doses) and tocilizumab (every four weeks).

Summary of comparative health economic evidence

The manufacturer presented a lifetime cost-utility analysis comparing certolizumab pegol plus methotrexate (MTX) to etanercept plus MTX or adalimumab plus MTX or infliximab plus MTX in patients with moderate to severe active rheumatoid arthritis who have failed on conventional DMARD therapy. The analysis also compared certolizumab pegol monotherapy to etanercept or adalimumab monotherapy. These comparators appeared reasonable, in particular to etanercept which was noted by SMC experts as being commonly used. Response within the model was assessed by ACR criteria and patients who failed to achieve a response with these treatments could move through a sequence of other drugs such as sulfasalazine, leflunomide or gold. The manufacturer also provided a cost-minimisation analysis.

Clinical data underpinning the model came from a mixed treatment comparison (MTC) and the manufacturer concluded that certolizumab pegol plus MTX was at least as effective as adalimumab, etanercept and infliximab in combination with MTX. The manufacturer stated that the results of the MTC also indicated that certolizumab pegol was at least as effective as adalimumab and etanercept when used as monotherapies. In both cases the MTC showed some non-significant advantages of certolizumab pegol. For the monotherapy model, it should be noted that clinical data for certolizumab pegol were based on the unlicensed maintenance regimen of 400mg every four weeks.

Patients in the model who achieved a response to treatment with certolizumab pegol or the comparator treatments were assumed to maintain the response for just over 3 years on the basis of a published study. The initial achievement of an ACR 20, 50 or 70 response gave rise to an improvement in utility which was estimated directly from EQ-5D data from the pivotal studies. Response in the base case model was assessed at six months. During the period of continued response, utility was assumed to improve by 0.0202 per year, as estimated from an unpublished UCB analysis. Resource use was estimated from published studies. A patient access scheme was submitted by the manufacturer and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a simple discount was applied to the cost of certolizumab pegol.

The base case without PAS results indicated below:

	Incremental cost	**Incremental quality adjusted life year (QALY)**	**Incremental cost effectiveness ratio (ICER)**
Certolizumab pegol + MTX versus;			
(a) etanercept + MTX	£4,323	0.1	£44,917
(b) adalimumab + MTX	£2,944	0.24	£12,432
(c) infliximab + MTX	-£7,788	0.43	Certolizumab pegol dominates infliximab
Certolizumab pegol monotherapy versus:			
(a)adalimumab monotherapy	£1,256	0.27	£4,207
(b) etanercept monotherapy	£114	-0.07	Etanercept dominates certolizumab pegol

The cost-minimisation analysis indicated that certolizumab pegol would only be the preferred treatment in the comparison with infliximab plus MTX. One way sensitivity analysis showed that the result was most stable for the comparison with infliximab, where dominance was generally maintained. For the other comparisons the results were less stable, in particular to assumptions about quality of life progression with continued treatment.

When the PAS was applied, the following results were generated:

	Incremental cost	**Incremental QALY**	**ICER**
Certolizumab pegol + MTX versus;			
(a) etanercept + MTX	£2,786	0.1	£28,947
(b) adalimumab + MTX	£1,407	0.24	£5,942
(c) infliximab + MTX	-£9,324	0.43	Certolizumab pegol dominates infliximab
Certolizumab pegol monotherapy versus:			
(a)adalimumab monotherapy	-£54	0.27	Certolizumab pegol dominates adalimumab
(b) etanercept monotherapy	-£1,382	-0.07	Certolizumab pegol cheaper but less effective than etanercept

In the cost-minimisation analysis with the PAS, certolizumab pegol would be the preferred treatment against all the comparators listed.

Provision of the full details of the MTC was an advance on the previous submission, and this was generally well conducted, albeit showing wide credible intervals. However as noted in the clinical effectiveness section above, the analysis did exclude one certolizumab pegol study, which if it had been included, would have lowered the estimate of effect of certolizumab pegol. Additional analysis was provided by the manufacturer to show the impact of including this study, while noting that the study was not based on the licensed dosing of certolizumab pegol. In both the with- and without- PAS scenarios, this resulted in etanercept dominating certolizumab pegol when used as a combination treatment. Provision of results based on a cost-minimisation analysis was also helpful given that the results of the MTC suggested that the differences for certolizumab pegol were non-significant.

Summary of patient and public involvement

A Patient Interest Group Submission was made by National Rheumatoid Arthritis Society.

Additional information: guidelines and protocols

In January 2010 guidelines on eligibility criteria for the first biological therapy in RA were published jointly by the British Society of Rheumatology and British Health Professionals in Rheumatology. The preparation of these guidelines predates the licence of certolizumab pegol.

In February 2009 the National Institute for Health and Clinical Excellence published a clinical guideline (CG79) on the management of rheumatoid arthritis in adults. It recommends the use of the tumour necrosis factor alpha inhibitors adalimumab, etanercept and infliximab as options for the treatment of adults who have active rheumatoid arthritis as measured by DAS28 greater than 5.1 confirmed on at least two occasions, one month apart and have undergone trials of two DMARDs, including methotrexate (unless contraindicated). This guideline predates the licence of certolizumab pegol.

The European League against Rheumatism recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs were published online in May 2010. They recommend that in patients responding insufficiently to methotrexate and/or other synthetic DMARDs with or without glucocorticoids, biological DMARDs should be started; current practice would be to start a TNF inhibitor (adalimumab, certolizumab, etanercept, infliximab) which should be combined with methotrexate.

Additional information: comparators

Comparators are the tumour necrosis factor (TNF)-α inhibitors, adalimumab, etanercept, infliximab plus the interleukin inhibitor, tocilizumab.

Cost of relevant comparators

Drug	Dose Regimen	Cost Per Year (£)
Certolizumab pegol	**400mg subcutaneously at weeks 0, 2 and 4, then 200mg every 2 weeks**	**10,368 for first year then 9,295 for subsequent years**
Infliximab	3 mg/kg by intravenous infusion at weeks 0, 2, and 6, then every 8 weeks thereafter	*10,071 for first year then 8,812 for subsequent years
tocilizumab	8mg/kg by intravenous infusion once every 4 weeks	*9,984
Adalimumab	40mg subcutaneously every two weeks	9,295
Etanercept	25mg subcutaneously twice weekly or 50mg subcutaneously once weekly	9,295

Doses are for general comparison and do not imply therapeutic equivalence. Costs of certolizumab and etanercept from eVadis on 28 June 2010. Costs of adalimumab, infliximab and tocilizumab from MIMS June 2010. *Cost based on 70kg body weight

Additional information: budget impact

Without the PAS
The manufacturer estimated the net budget impact as £60k in year one rising to £80k in year five. These figures took account of drug costs and also administration and monitoring costs.
The net drug budget impact was £50k in year one and £170k in year five. These estimates related to the use of combination treatments only.

With the PAS
The manufacturer estimated a net budget impact of £20k in year one and a saving of £60k in year two rising to a saving of £200k by year five. These figures took account of drug costs, drug administration and monitoring costs. The net drug budget impact was £20k in year one, a saving of £30k in year two and a saving of £110k in year five. Again these estimates related to the use of combination treatments only.

For both sets of estimates the manufacturer estimated that over the next five years the eligible patient population would rise from 2,584 patients to 3,454 patients and it was assumed that all eligible patients would be treated with certolizumab pegol, adalimumab, etanercept or infliximab.

The manufacturer assumed an uptake of certolizumab pegol as a combination therapy of 1.7% in year one rising to 12% by year five. This market share was acquired from all three comparator treatments but to a greater extent from reduced prescribing of etanercept. The budget impact estimates did not include any estimate of the impact of certolizumab pegol in the monotherapy indication and were based on newly presenting patients only i.e. assumed no patients would be switched from existing TNF-α inhibitors to certolizumab pegol.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission

Keystone E, Heijde DV, Mason D, Jr, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: Findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 2008; 58(11): 3319-3329

Smolen JS, Landewe RB, Mease PJ, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: The RAPID 2 Study. Ann Rheum Dis 2009; 68:797-804

The European Medicines Agency (EMA) European Public Assessment Report. Certolizumab pegol (Cimzia®) Procedure No. EMEA/H/C/001037 2009 http://www.emea.europa.eu/

This assessment is based on data submitted by the applicant company up to and including 11 August 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.