Scottish Medicines Consortium

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

UCB Pharma Ltd

09 April 2010 *(Issued 07 May 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 full submission

certolizumab pegol (Cimzia®) is not recommended for use within NHS Scotland.

Licensed 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 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.

However, the manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The licence holder has indicated their intention to resubmit.

Overleaf is the detailed advice on this product.

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.

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.

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.

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 studies that compared two doses of certolizumab pegol with placebo in patients also receiving methotrexate and a third study that compared certolizumab pegol monotherapy with placebo.

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 every 2 weeks thereafter, or certolizumab pegol 400mg at weeks 0, 2, and 4 followed by 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.

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 in the modified total Sharp score (mTSS) at week 52. 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 decrease 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.

In both studies, compared with placebo, ACR50 and ACR70 response rates were significantly higher with certolizumab pegol as was 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.

A randomised, double-blind, placebo-controlled study of certolizumab pegol as monotherapy had similar inclusion criteria 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 1 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 were mild or moderate in intensity. Infections were the most frequent adverse events (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 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.

Summary of clinical effectiveness issues

Certolizumab pegol has not been directly compared with other drugs in patients with rheumatoid arthritis. An indirect comparison with other TNF-α inhibitors using placebo as the common comparator suggested certolizumab pegol had similar efficacy but its validity could not be confirmed due to errors concerning the common comparator and a lack of transparency.

In the monotherapy study 400mg certolizumab was administered every four weeks. This dose regimen is not licensed.

Certolizumab pegol is a subcutaneous injection that is administered every two weeks. Self-administration after adequate training may be possible for some patients. This administration route and dosage interval may be beneficial. Comparators are adalimumab, administered subcutaneously every two weeks, etanercept, administered subcutaneously twice weekly, (once weekly is also permitted), infliximab, administered as an intravenous infusion every eight weeks (after initial loading doses) and the recently licensed tocilizumab, administered as an intravenous infusion every four weeks.

Summary of comparative health economic evidence

The manufacturer presented a lifetime cost-utility analysis comparing certolizumab pegol + methotrexate (MTX) to etanercept + MTX or adalimumab + MTX or infliximab + MTX.

The analysis also compared certolizumab pegol monotherapy to etanercept or adalimumab monotherapy. These comparators appeared reasonable. 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. Rituximab or sequential treatment with an alternative anti-TNF drug were not included as alternatives within the pathway.

Clinical data underpinning the model came from an indirect comparison and the manufacturer's analysis suggested that certolizumab pegol offered similar, or improved, ACR response rates to the comparator therapies. 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. 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.

The base case results indicated below:

	Incremental cost	**Incremental QALY**	**ICER**
Certolizumab + MTX versus;			
(a) etanercept + MTX	£2,993	0.065	£46,192
(b) adalimumab + MTX	£3,124	0.242	£12,937
(c) infliximab + MTX	-£6,441	0.458	Certolizumab dominates infliximab
Certolizumab monotherapy versus:			
(a) adalimumab monotherapy	£1,223	0.215	£5,687
(b) etanercept monotherapy	-£517	-0.13	£3,976

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.

There were a number of issues with the analysis:

- The main issue relates to some concerns with the indirect comparison method and results which are used to drive the model. The results of the analysis showed certolizumab pegol to have numerically superior ACR response rates to infliximab and adalimumab and improved ACR20 responses to etanercept combination therapy. However, some results lacked statistical significance and these were key drivers of the overall result. In general, the indirect comparison lacked transparency and statistical advice suggested that a mixed treatment comparison may have been a more appropriate methodology to have used.
- The duration of treatment was based on a published study and response was assumed to be maintained for the duration of treatment. Clearly long term data from certolizumab pegol trials is not yet available to confirm these assumptions, which are important within the model structure.

In response to these issues, the manufacturer provided some supplementary analysis. Analysis using a mixed treatment comparison gave a pattern of results similar to those described above. It should be noted however that limited information was provided to allow adequate appraisal of the mixed treatment methodology.

The manufacturer also provided a cost-minimisation analysis to show the impact of assuming certolizumab had the same, rather than better, ACR responses compared to the other treatments. The results indicated that certolizumab would be preferred to infliximab but not etanercept or adalimumab combination therapies. In the case of monotherapy, certolizumab would not be preferred on cost minimisation grounds.

Given the weaknesses above, the economic case was not considered demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was received from the National Rheumatoid Arthritis Society (NRAS).

Additional information: guidelines and protocols

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 disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, one month apart and have undergone trials of two disease-modifying anti-rheumatic drugs, including methotrexate (unless contraindicated). This guideline predates the licensing of certolizumab pegol.

British Society for Rheumatology guidance on the use of biologics in rheumatoid arthritis is currently being revised. In 2005 an update of previous 2001 guidelines stated: “There is no current evidence to suggest that any type of anti-TNF therapy is more efficacious than the others. Selection of an anti-TNF agent will be based on patient preference and practical issues relating to drug administration and delivery. Etanercept and adalimumab do not require co-prescription with methotrexate, so that this is an attractive option in patients intolerant of this drug.

Additional information: comparators

Comparators are the TNF-α inhibitors, adalimumab, etanercept, infliximab and tocilizumab.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
certolizumab	**400mg subcutaneously at weeks 0, 2 and 4, followed by a maintenance dose of 200mg every 2 weeks**	**10,725 for first year then 9,295 for subsequent years***
adalimumab	40mg subcutaneously every two weeks	9,295**
etanercept	25mg subcutaneously twice weekly or 50mg subcutaneously once weekly	9,295
infliximab	3 mg/kg# by intravenous infusion at weeks 0, 2, and 6, then every 8 weeks thereafter	10,071 for first year then 7553 for subsequent years**
tocilizumab	8mg/kg# by intravenous infusion once every 4 weeks	9,318 **

Doses are for general comparison and do not imply therapeutic equivalence. All drugs are given with methotrexate. Costs from eVadis on 26 September 2009 unless otherwise indicated. *Cost from submitting company. **Costs from MIMS September 2009. #Cost based on 70kg body weight.

Additional information: budget impact

The gross drug budget impact of introducing certolizumab pegol was estimated as £50k in year one rising to £3.37m in year five. The net effect, after taking account of monitoring and administration and the costs of the alternative treatments that would have been prescribed was a budget impact of zero in year one rising to a saving of £50k in year five.

These estimates assumed 2068 patients would be eligible to be treated with a biological DMARD in year one rising to 3125 patients by year five. Market share of the eligible patient population was estimated at 0.2% in year one rising to 11.5% by year five to give 4 patients treated in certolizumab pegol in year one rising to 360 by year five. Market share is mainly taken from etanercept or to a lesser extent infliximab. The manufacturer assumed that patients would be de novo patients and therefore does not assume any switching of patients from existing treatments after failure of an anti-TNF.

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.

This assessment is based on data submitted by the applicant company up to and including ***17 March 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.

The undernoted references were supplied with the submission.

Fleischmann R, Vencovsky J, van VR, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis 2009; 68:805-11

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