Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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certolizumab pegol 200mg/mL solution for injection in pre-filled syringe (Cimzia®)

SMC No. (960/14)

UCB Pharma UK

04 April 2014

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 accepted for use within NHS Scotland.

Indication under review: Certolizumab pegol is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising:

- Ankylosing spondylitis (AS)

Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs).

- Axial spondyloarthritis without radiographic evidence of AS (nr-axSpA)

Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs.

In a randomised double-blind study, conducted in axial spondyloarthritis patients, including AS and nr-axSpA patients, there was a significantly higher proportion of Assessment of SpondyloArthritis International Society 20% responders at week 12 for certolizumab pegol- compared to placebo-treated patients.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of certolizumab. This SMC advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 12 May 2014

Indication

Certolizumab pegol is indicated for the treatment of adult patients with severe active axial spondyloarthritis (axSpA), comprising:

- Ankylosing spondylitis (AS)

Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs).

- Axial spondyloarthritis without radiographic evidence of AS (nr-axSpA)

Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated CRP and /or MRI, who have had an inadequate response to, or are intolerant to NSAIDs.

Dosing Information

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which certolizumab pegol is indicated. Patients should be given the special alert card.

The recommended starting dose of certolizumab pegol for adult patients is 400mg (given as two subcutaneous injections of 200mg each) at weeks 0, 2 and 4.

After the starting dose, the recommended maintenance dose of certolizumab pegol for adult patients with axial spondyloarthritis is 200mg every 2 weeks or 400mg every 4 weeks.

Product availability date

December 2013

Summary of evidence on comparative efficacy

Axial spondyloarthritis (axSpA) refers to spondyloarthropathy with predominantly axial involvement and comprises the disease subgroups of ankylosing spondylitis (AS) and axial spondyloarthritis without radiographic evidence of AS (nr-axSpA). Certolizumab pegol is a humanised fragment antigen binding prime (Fab′) conjugated to polyethylene glycol (PEG) which neutralises human tumour necrosis factor (TNF)-α bioactivity and inhibits the production of inflammatory cytokine by monocytes.[1] This submission relates to a license extension for use in the treatment of AS and nr-axSpA.[2]

One phase III, parallel group, double-blind, placebo-controlled 24-week study (RAPID-axSpA) recruited patients aged ≥18 years with chronic back pain for ≥3 months and who fulfilled the Assessment of SpondyloArthritis International Society (ASAS) criteria for axSpA.[1,3] Patients must have previously had an inadequate response, or been intolerant, to ≥1 NSAID during ≥30 days of continuous therapy (highest tolerated dose) or ≥2 weeks each for ≥2 NSAIDs. Previous treatment with one anti-TNF therapy was permitted, though those with primary failure to the anti-TNF therapy were excluded. To obtain a broadly balanced population of AS and nr-axSpA patients in the study, at least 50% had to satisfy modified New York (mNY) criteria in addition to ASAS criteria.

Patients were randomised equally to subcutaneous (sc) injection of certolizumab pegol 200mg every two weeks (“certolizumab pegol 200mg Q2W” group, n=111), certolizumab pegol 400mg every four weeks (“certolizumab pegol 400mg Q4W” group, n=107) both after a starting regimen of certolizumab

pegol 400mg at weeks 0, 2 and 4) or placebo (sodium chloride 0.9%) (n=107). Randomisation was stratified by site, fulfilment of mNY criteria (yes/no) and prior anti-TNFα exposure (yes/no). A total of 56 patients (52%) in the placebo group did not achieve an ASAS20 response at weeks 14 and 16, underwent mandatory escape at week 16, and were randomised to certolizumab pegol 200mg every two weeks (n=27) or 400mg every four weeks (n=29). In the certolizumab pegol 200mg Q2W and certolizumab pegol 400mg Q4W groups, 35 (32%) and 25 (23%) patients fulfilled the escape criteria but continued on their original treatment.

The primary endpoint, ASAS20 response at week 12, was defined as an improvement of ≥20% and ≥1 unit on a 0 to 10 numerical rating scale (NRS) in ≥3 of the following domains; Patient's Global Assessment of Disease Activity (PtGADA); pain assessment (total spinal pain NRS score); function (represented by Bath Ankylosing Spondylitis Functional Index [BASFI]) and inflammation (mean of Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] questions 5 and 6 relating to morning stiffness) and no deterioration (worsening of ≥20% or 1 NRS unit) in the remaining domain. The proportion of patients achieving the primary endpoint was 58% in the certolizumab pegol 200mg Q2W group, 64% in the certolizumab pegol 400mg Q4W group and 38% in the placebo group. The difference for certolizumab pegol 200mg Q2W versus placebo was 19% (95% confidence interval [CI] 6.3% to 32%); p=0.004 and for certolizumab pegol 400mg Q4W versus placebo was 25% (95% CI 12% to 38%); p<0.001. The number of patients classified as having AS was 178 and nr-axSpA was 147. There were statistically significant differences for the combined certolizumab pegol group over placebo in the subgroups of patients with AS (24% [95% CI 8.2% to 39%]; p=0.003) and nr-axSpA (21% [95% CI 4.1% to 38%]; p=0.017).

Secondary endpoints included ASAS20 at week 24; and change from baseline in BASFI, BASDAI, Bath Ankylosing Spondylitis Metrology Index (BASMI) linear and ASAS40 at week 12 and 24. Both dose regimens of certolizumab pegol were statistically significantly superior to placebo for these secondary endpoints (p<0.05 at week 12 and p<0.001 at week 24).

The study was dose-blind from week 24 to 48 and open-label to week 204. At week 24, patients originally randomised to certolizumab pegol continued treatment and patients in the placebo group were re-randomised to certolizumab pegol 200mg every two weeks or 400mg every four weeks (or at week 16 for non-responders). Results up to week 48 have been published for the 218 patients originally randomised to certolizumab pegol.[4] Of these patients, 93% completed week 24 and 88% completed week 48. At week 48, the proportion of ASAS20 responders was 71% and 72% for the certolizumab pegol 200mg Q2W and certolizumab pegol 400mg Q4W groups respectively and ASAS40 responders were 53% and 62%. For the certolizumab pegol 200mg Q2W and certolizumab pegol 400mg Q4W groups respectively, baseline mean BASDAI scores were 6.49 and 6.39, and BASFI scores were 5.26 and 5.40. At week 48, the mean BASDAI score was 3.1 for both certolizumab pegol groups and the mean BASFI score was 2.6 and 3.0 for certolizumab pegol 200mg Q2W and certolizumab pegol 400mg Q4W groups respectively. At baseline, mean BASMI linear scores were 3.71 and 3.81 for the certolizumab pegol 200mg Q2W and certolizumab pegol 400mg Q4W groups respectively. The mean BASMI linear score at week 48 was 3.0 for certolizumab pegol 200mg Q2W and 3.2 for certolizumab pegol 400mg Q4W.

Summary of evidence on comparative safety

No comparative safety data, except versus placebo, are available. Refer to the summary of product characteristics for full details of adverse events (AE).[2]

The most common infectious AE reported in the placebo-controlled, double-blind phase of the study were nasopharyngitis (10% [22/218] certolizumab pegol [combined group] versus 6.5% [7/107] placebo) and upper respiratory tract infection (4.6% [10/218] certolizumab pegol versus 2.8% [3/107] placebo). There were two serious infections (haemophilus infection and laryngitis) in the certolizumab pegol 200mg group versus none in the other groups. The most common non-infectious AE were headache (6.2% certolizumab pegol versus 6.5% placebo) and increased blood creatine phosphokinase (5.1% certolizumab pegol versus 1.9% placebo) which were transient, resolved spontaneously despite continued certolizumab pegol treatment, and were often considered by investigators as possibly related to increased physical activity.[3]

No opportunistic infections (including tuberculosis [TB]) were reported up to week 24. In the dose-blind phase serious infections occurred in 10 (3.2%) patients, including suspected TB in three patients of which one was confirmed.[4] No malignancies or deaths were reported up to week 48.

Summary of clinical effectiveness issues

The recommended treatments for axSpA are NSAIDs or anti-TNF drugs. In addition to certolizumab pegol, etanercept, adalimumab, golimumab and infliximab are licensed for the treatment of AS, although infliximab has not been recommended for this indication by the National Institute for Health and Care Excellence (NICE).[5] There are limited licensed anti-TNF treatments for nr-axSpA, with only certolizumab pegol and adalimumab having marketing authorisation for this population.

In the pivotal study there were statistically significant differences for certolizumab pegol (pooled) and individual dose regimens versus placebo for the primary end-point, ASAS20 at week 12. Results of the secondary end-points were supportive of the primary end-point. The proportion of ASAS20/ASAS40 responders and improvements from baseline in BASDAI, BASFI and BASMI linear were maintained up to week 48. The study included AS and nr-axSpA patients with significant disease burden. No differences in efficacy or safety were seen between the two dose regimens of certolizumab pegol used in the study and both are licensed.[1]

European Medicines Agency (EMA) guidance notes that for drugs other than NSAIDs a higher improvement in ASAS (e.g. ASAS40) may be required.[6] While ASAS20 was the primary endpoint in the pivotal study, ASAS40 was included as a secondary endpoint and a statistically significant result for certolizumab pegol relative to placebo was also demonstrated. The EMA highlighted an issue in terms of misclassification of the AS and nr-axSpA subgroups in the study.[1] It appeared that a number of patients in the nr-axSpA subgroup actually fulfilled AS criteria and vice versa. Consequently the EMA raised concerns regarding limitations with the subgroup analysis of nr-axSpA and AS patients. However, a post hoc analysis based on central reading of baseline x-rays showed similar results to the initial subgroup analysis.

There are no comparative efficacy data other than versus placebo. The submitting company conducted a mixed treatment comparison (MTC) in the AS sub-population which compared certolizumab pegol with adalimumab, golimumab and etanercept at week 24 for a number of outcomes including ASAS20, ASAS40, BASDAI and BASFI. There were no statistically significant

differences between certolizumab pegol and active comparator for any of these outcomes. For the nr-axSpA sub-population, a fixed effect MTC, comprising two studies, compared certolizumab pegol with adalimumab at week 12 (the duration of the double-blind part of the adalimumab study). There were no statistically significant differences between treatments for outcomes with the exception of change in BASDAI, BASFI and PtGADA where certolizumab pegol was significantly superior to adalimumab. There was heterogeneity in the patient populations between the studies. However, overall certolizumab pegol was considered to be broadly comparable with comparators in the MTCs conducted in the AS and nr-axSpA sub-populations.

Clinical experts consulted by SMC considered certolizumab pegol would be used as an alternative to other anti-TNF agents, with cost, administration frequency and injection device informing a decision. After training in injection technique, patients may self-inject using the pre-filled syringe if the patient's physician determines that it is appropriate and with medical follow-up as necessary. Patients should carry an alert card in which results of screening tests (tuberculin skin test and chest X-ray) should be recorded. [2]

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The company submitted two economic evaluations, one for AS and one for nr-axSpA. Both were cost-utility analyses and both used a dual structure for the model with a decision tree to represent the initial treatment division into a response or not, followed by a Markov structure for the longer-term impact on the disease. The model also allowed mortality rates in excess of the population norm to be included.

The comparators in the AS model were etanercept, adalimumab and golimumab. In the nr-axSpA group the main comparator was adalimumab. In each case, 'conventional care' was also considered but this is less relevant in Scottish practice. The clinical data used in the model came from the MTCs described above. Differences between treatments in terms of response rates were used in the model, irrespective of whether the differences were significant. The data from the MTCs were extrapolated assuming that if patients stayed on treatment they would have the same response rate. The time horizon was the lifetime of the patient; this was limited to 20 years in a sensitivity analysis.

Utility values were based on equations linking BASDAI and BASFI to EQ-5D in the main clinical study; this allowed the company to predict utility values where BASDAI and BASFI went outside the range seen in the main study. Resource use included medicines costs and costs of training patients to carry out self-injection. Costs of on-going care were also included based on previous health technology assessments of this condition.

The company submitted a Patient Access Scheme (PAS) which was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS was a simple discount which lowered the list price of certolizumab.

Taking adalimumab as the main comparator, the results with the PAS showed certolizumab was the dominant treatment (i.e. more effective and less costly) in both the AS sub-population and the nr-axSpA sub-population. Scenario analysis, one-way sensitivity analysis and probabilistic analysis were all provided. The main findings were that changing efficacy rates and medicines costs made a difference to results. This was not surprising, given the small differences between treatments.

The following weaknesses were noted:

- No direct comparative data were available. Therefore, MTCs were required to compare

certolizumab pegol with current treatments for both sub-populations.

- The submitting company did not present a simple cost-minimisation analysis but instead continued to full cost-utility analysis using absolute differences in response rates from the MTCs despite lack of evidence these were statistically or clinically significant. However, a cost-minimisation analysis was subsequently provided as noted below.
- The treatment sequence is only one anti-TNF, then NSAIDs – this may be overly simple but given the lack of differences between anti-TNFs the added complexity would have been unnecessary.

In response to a request from SMC reviewers, the company submitted revised analysis that excluded differences in endpoints that did not achieve statistical significance in the MTCs, and this was taken into account as follows:

(i) In the ankylosing spondylitis (AS) sub-population, a cost-minimisation was presented which showed there was a net saving when the PAS was included.

(ii) In the nr-SpA sub-population, a cost-utility analysis was presented based on statistically significant differences in BASDAI and BASFI scores only. With the PAS certolizumab was estimated to be dominant over adalimumab. The company also presented a cost-minimisation analysis versus adalimumab in this patient group, which showed certolizumab to be cost-saving with the PAS.

The additional analysis was helpful. The Committee agreed that in the ankylosing spondylitis sub-population there was an adequate basis for the MTC and the cost-minimisation showed that with the PAS there could be a small saving for an equivalent outcome. As such, the economic case was demonstrated in this group.

The nr-axSpA sub-population required more discussion since the evidence network for the MTC only had two randomised controlled trials.(RCTs) The Committee recognised there were issues for a company in building an adequate evidence network where only a limited number of previous RCTs were available. Combining these points with the evidence from the cost-minimisation analysis, the Committee felt on balance the economic case was demonstrated.

It is SMC policy to include the estimated QALY gain in the detailed advice document for all submissions. The PAS for certolizumab includes a discount to the NHS that is commercial in confidence and the submitting company has advised that publication of the QALY gain, when considered with other cost-effectiveness data in the public domain, could reveal the level of discount. For this reason SMC has agreed not to publish the estimated QALY gain.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specified Patient Information Group.

- A submission was received from the National Ankylosing Spondylitis Society (NASS), a registered charity.
- NASS has received funding from several pharmaceutical companies in the past two years.
- Ankylosing spondylitis (AS) is an inflammatory condition of the spine that often produces pain, stiffness, deformity and disability throughout adult life; a chronic progressive disease characterised by periods of fluctuating intensity, leading to slowly increasing spinal and

peripheral joint damage. The key symptom in early disease is inflammatory back pain. AS is frequently associated with disorders at sites distant from the spine including iritis, psoriasis and inflammatory bowel disease. There is an increased risk of premature death from cardiovascular disease in particular.

- Many people with AS suffer from depression, fatigue and poor sleep which exert a profound influence on their quality of life. A proportion of individuals may require major joint or spinal surgery.

- Current treatments may not provide relief, or patients may be unable to take due to concomitant problems being exacerbated by them. Certolizumab has the advantage of offering patients the choice of an alternative option for this illness.

Additional information: guidelines and protocols

NICE multiple technology appraisal 143; Adalimumab, etanercept and infliximab for ankylosing spondylitis was published in May 2008 (reviewed October 2010).[5] The following was recommended:

- Adalimumab or etanercept are recommended as treatment options for adults with severe active ankylosing spondylitis only if all of the following criteria are fulfilled.
    - The patient's disease satisfies the modified New York criteria for diagnosis of ankylosing spondylitis.
    - There is confirmation of sustained active spinal disease, demonstrated by:
        - a score of at least 4 units on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and
        - at least 4 cm on the 0 to 10 cm spinal pain visual analogue scale (VAS).

    These should both be demonstrated on two occasions at least 12 weeks apart without any change of treatment.
    - Conventional treatment with two or more non-steroidal anti-inflammatory drugs taken sequentially at maximum tolerated or recommended dosage for 4 weeks has failed to control symptoms.
- Infliximab is not recommended for the treatment of ankylosing spondylitis.

ASAS published a 2010 update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis in 2011.[7] All patients should have tried a minimum of two NSAIDs at maximum recommended dose for a minimum of four weeks in total, unless contraindicated. Pre-treatment with a disease modifying anti-rheumatic drug is not required in patients with predominately axial manifestations. All patients with axial SpA should be considered for the use of an anti-TNF agent as the burden of disease is similar in patients with radiographic and non-radiographic SpA and the efficacy of anti-TNF drugs was considered similar. Anti-TNF therapy should be continued for at least 12 weeks to assess for response.

Additional information: comparators

Etanercept, adalimumab and golimumab for AS and adalimumab for nr-axSpA.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Certolizumab pegol	**200mg sc every two weeks or 400mg every four weeks**	**9,295****
Golimumab*	50mg or 100mg sc once monthly	9,156 to 18,311
Etanercept*	25mg sc twice weekly or 50mg sc once weekly	9,295
Adalimumab	40mg sc every other week	9,156

Doses are for general comparison and do not imply therapeutic equivalence. Costs are from eVadis or MIMS on 21/1/14. Costs do not take any patient access schemes into consideration. sc=subcutaneous
*licensed for AS only
**cost of certolizumab pegol in year one is £10,725 (400mg given on weeks 0, 2 and 4).

Additional information: budget impact

Without the PAS, the submitting company estimated the gross impact on the medicines budget to be £1.42m in year 1 and £4.41m in year 5. As other drugs were assumed to be displaced, the net drug budget impact was estimated to be £162k in year 1 and £143k in year 5.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. European Medicines Agency. European Public Assessment Report for certolizumab pegol (Cimzia). EMA/CHMP/458168/2013. 19 September 2013

2. UCB Pharma UK. Summary of product characteristics for certolizumab pegol (Cimzia®). Last updated November 2013.

3. Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled phase 3 study. Ann Rheum Dis 2014; 73: 39-47

4. Landewé RB, Rudwaleit M, van der Heijde DM, et al. Effect of certolizumab pegol over 48 weeks in patients with axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis. ACR 2013 poster abstract accepted.

5. NICE multiple technology appraisal guidance 143; Adalimumab, etanercept and infliximab for ankylosing spondylitis. May 2008

6. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of ankylosing spondylitis. CPMP/EWP/4891/03. 23 April 2009.

7. van der Heijde D, Sieper J, Maksymowych WP, et al. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis 2011; 70(6): 905-8.

This assessment is based on data submitted by the applicant company up to and including 14 March 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. 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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.