PUBLIC SUMMARY DOCUMENT

Product: CERTOLIZUMAB PEGOL, injection, 200 mg in 1 mL, single use pre-filled syringe, Cimzia®

Sponsor: UCB Australia Pty Ltd

Date of PBAC Consideration: March 2010

1. Purpose of Application

The submission sought an Authority required listing for the treatment of severe active rheumatoid arthritis in adult patients who meet certain criteria.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Certolizumab was registered with the Therapeutic Goods Administration (TGA) on 22 December 2009 for the treatment of moderate to severe active rheumatoid arthritis in adult patients,

- combined with methotrexate in case of either an inadequate response or intolerance to previous therapy with one or more disease-modifying antirheumatic drugs (DMARDS), or
- as monotherapy in case of a contraindication or intolerance to methotrexate

4. Listing Requested and PBAC's View

The following is an abbreviated version of the listing requested:

Authority Required

Initial 1 (new patients)

Application for initial PBS-subsidised treatment with certolizumab pegol, by a rheumatologist or clinical immunologist with expertise in the management of rheumatoid arthritis, of adults who:

a) have severe active rheumatoid arthritis; and

b) have received no prior PBS-subsidised treatment with a bDMARD for this condition in this treatment cycle; and

c) have failed to achieve an adequate response to the following treatments:
   - i. methotrexate at a dose of at least 20 mg weekly; and
   - ii. methotrexate (at a minimum dose of 7.5 mg weekly), in combination with 2 other non-biological disease modifying anti-rheumatic drugs (DMARDs), for a minimum of 3 months; and
   - iii. a minimum of 3 months' treatment with:
     1. leflunomide alone; or
     2. leflunomide in combination with methotrexate; or
     3. cyclosporin.

The following initiation criteria indicate failure to achieve an adequate response and must be demonstrated in all patients at the time of the initial application:

1. an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour or a C-reactive protein (CRP) level greater than 15 mg per L;
   AND either
2. a total active joint count of at least 20 active (swollen and tender) joints; or
3. at least 4 active joints from the following list of major joints:

- elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or
- shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth).

All tests and assessments should be performed preferably whilst still on treatment, but no longer than 1 month following cessation of the most recent prior treatment.

Assessment of a patient's response to an initial course of treatment must be made after at least 12 weeks of treatment so that there is adequate time for a response to be demonstrated. This assessment, which will be used to determine eligibility for continuing treatment, must be submitted to Medicare Australia no later than 1 month from the date of completion of this initial course of treatment. Where a response assessment is not undertaken and submitted to Medicare Australia within these timeframes, the patient will be deemed to have failed to respond to treatment with certolizumab pegol.

Authority Required
Continuing treatment
Following the completion of an initial treatment course with a specific bDMARD, a patient may qualify to receive up to 24 weeks of continuing treatment with that drug providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing bDMARD treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response.

It is recommended that a patient be reviewed in the month prior to completing their current course of treatment to ensure uninterrupted bDMARD supply.

Assessments of response to a course of PBS-subsidised therapy must be submitted to Medicare Australia no later than 4 weeks from the date that course was ceased. Where a response assessment is not submitted to Medicare Australia within these timeframes, the patient will be deemed to have failed to respond to treatment with that bDMARD.

The PBAC considered that the requested restriction and interchangeability criteria for certolizumab should be identical to those of adalimumab but would also need to incorporate the changes recommended at the December 2009 special PBAC meeting for all PBS listed biological disease modifying anti-rheumatic drugs (bDMARDs) for rheumatoid arthritis. *See Recommendation and Reasons.*

5. Clinical place for the proposed therapy

Rheumatoid arthritis is an inflammatory disorder, typically featuring a combination of peripheral symmetrical inflammatory arthritis and a number of well-described extra-articular symptoms. It is associated with significant morbidity, disability and mortality.

Certolizumab would provide another bDMARD treatment option for adult patients with severe active rheumatoid arthritis.

6. Comparator

The submission nominated adalimumab as the main comparator. The PBAC accepted that this was an appropriate comparator.

7. Clinical Trials

The submission presented an indirect comparison of certolizumab (given in combination with methotrexate) with adalimumab (given in combination with methotrexate) based on six randomised comparative trials using placebo as the common comparator. Five of these six trials had been published at the time of submission, as shown in the table below. An indirect comparison in the monotherapy setting (certolizumab or adalimumab given alone) was also presented and was based on three randomised comparative trials using placebo as the common comparator.

The published trials presented in the submission are shown as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
With methotrexate		
CPD870-027 (RA-I Rapid1) Keystone et al. (2008)	CDP870-027 Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis.	October 2007 *Arthritis & Rheumatism* 2008, 58(11): 3319-3329.
CDP870-050 (RA-II: Rapid2) Smolen et al. (2008)	CDP870-050 Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomized control trial.	October 2007 *Ann Rheum Dis* doi: 2008, 10.1136(2009; 68(6): 797-804)
Adalimumab plus methotrexate		
Weinblatt et al. (2003)	Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: The ARMADA trial.	*Arthritis Rheum* 48(1): 35-45.
Keystone et al. (2004)	Radiographic, clinical and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy.	*Arthritis Rheum* 2004, 50(5): 1400-1411
Kim et al. (2007)	A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered sub-cutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate.	*Journal of Rheumatology* 2007, 10:9-16
Monotherapy		
CDP870-011 (RA-III FAST4WARD) Fleischmann et al. (2009)	CDP870-011 Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST 4WARD study.	July 2006 *Ann Rheum Dis* 2009, 686 805-811
Van de Putte et al. (2004)	Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed.	*Ann Rheum Dis* 2004, 63(5): 508-516
Miyasaka et al.	Clinical investigation in highly disease-affected	*Mod Rheumatol*

(2008)	rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study	2008, 18252-262

8. Results of Trials

The submission presented indirect comparisons using the American College of Rheumatology (ACR) 20/50/70 responses at 12, 14/16 and 24/26 weeks as the measure of outcome, and the indirect odds ratio (OR), relative risk (RR) and risk difference (RD) as the analytical measures. The submission nominated the indirect OR as the preferred analytical measure and 12 weeks as the preferred endpoint.

At the submission's preferred time point of 12 weeks, all indirect comparisons showed no statistically significant difference between certolizumab and adalimumab for either dosage regimen in the plus methotrexate setting, or in the monotherapy setting.

There was also no statistically significant difference at 14/16 weeks and 24 weeks, for the certolizumab 200 mg given once every 2 weeks (Q2W) (after loading doses) plus methotrexate regimen. However, for the certolizumab 400 mg given once every 4 weeks (Q4W) plus methotrexate regimen at 24 weeks, statistically significant differences favouring adalimumab were observed for the ACR70 based on the indirect OR (and RR, RD); for the ACR50 based on the indirect RR and RD; and for the ACR20 based on the indirect RD. In addition, there was a non-significant trend favouring adalimumab for some of the measures/time points.

For the certolizumab 400 mg Q4W monotherapy regimen, a statistically significant difference favouring adalimumab was observed in ACR70 response at 14/16 weeks for the indirect RD (-0.071 95 % CI -0.131, -0.011).

The submission also presented a number of backward step indirect comparisons, excluding some of the trials with less comparable characteristics (one certolizumab trial with a lower mean methotrexate dose (i.e. CDP870-050) and/or two adalimumab trials undertaken in Asian populations (i.e. Kim et al. 2007, Miyasaka et al. 2008). For the certolizumab 200 mg Q2W (after loading) plus methotrexate regimen, the backward step analysis excluding Kim et al. (2007) showed a statistically significant difference favouring certolizumab based on the indirect OR (and indirect RR, RD) for the ACR20 at 12 weeks. No statistically significant differences were observed in an analysis excluding Kim et al. (2007) and CDP870-050.

For the certolizumab 400 mg Q4W monotherapy regimen, the backward step analysis excluding Miyasaka et al. (2008) exhibited five statistically significant differences (two favouring certolizumab and three favouring adalimumab – including two favouring adalimumab at the submission's preferred 12 week time point). However, none were based on the submission's preferred analytical measure of the indirect OR.

The PBAC noted that the only certolizumab trials that were consistent with the TGA recommended doses were trials CDP870-027 and CDP870-050 which used a 400 mg loading doses at 0, 2 and 4 weeks followed by 200 mg every two weeks and where methotrexate was given concomitantly. On the totality of the evidence, the PBAC accepted that certolizumab plus methotrexate and as monotherapy was non inferior to adalimumab in terms of comparative effectiveness at the recommended TGA dose (400 mg loading dose with a 200 mg biweekly or 400 mg four weekly maintenance dose).

The submission did not provide any comparison from the clinical trials (as an indirect analysis or as a descriptive summary) of safety outcomes for certolizumab versus adalimumab. This did not permit any assessment of the comparative safety of certolizumab to be made. The submission addressed an extended assessment of safety using information from three open-label extension studies of certolizumab, a Periodic Safety Update report for certolizumab, an integrated safety report for certolizumab, an open label extension study for adalimumab, and the relevant Product Information (PI). The submission concluded that the pattern and incidence of adverse events with certolizumab is consistent with that observed in rheumatoid arthritis RA patients treated with other tumour necrosis factor (TNF) inhibitor therapy.

The PBAC noted that while no formal indirect comparisons of adverse event data for certolizumab and adalimumab was presented in the submission, the sponsor in its pre-PBAC advice provided an indirect comparison of key safety outcomes based on absolute numbers which indicated that there was no evidence of differences in the pattern and incidence of adverse events in rheumatoid arthritis patients treated with certolizumab to currently listed anti TNF agents.

9. Clinical Claim

The submission described certolizumab as non-inferior to adalimumab in terms of comparative effectiveness.

On the totality of the evidence, the PBAC accepted that certolizumab plus methotrexate and as monotherapy was non inferior to adalimumab in terms of comparative effectiveness at the recommended TGA dose (400 mg loading dose with a 200 mg biweekly or 400 mg four weekly maintenance dose).

10. Economic Analysis

The submission presented a single cost-minimisation analysis to cover both the plus methotrexate and monotherapy settings, based on a certolizumab dose of 400 mg at weeks 0, 2 and 4 followed by 200 mg Q2W (or 400 mg Q4W). The use of (i) a loading dose with a 400 mg Q4W regimen, in either the plus methotrexate or in the monotherapy setting; or (ii) a 200 mg Q2W regimen in the monotherapy setting, were not consistent with the clinical evidence presented by the submission.

The submission estimated no incremental cost associated with certolizumab (undiscounted estimate over 2 years assuming 67 % continuation rate). The proportion of responders of 67 % was not clearly justified by the submission. Further, during evaluation it became apparent that the submission under-estimated the usage of certolizumab in the continuation phase by 0.5 scripts. Thus the submission's analysis was likely to have underestimated the costs associated with certolizumab treatment.

11. Estimated PBS Usage and Financial Implications

The likely number of prescriptions dispensed/year was estimated to be less than 10,000 initiation scripts per year and between 10,000 to 50,000 continuation scripts per year in Year 5.

The financial cost/year to the PBS was estimated to be less than $10 million in Year 5. The estimate was based on 12.5 continuation scripts per year in Year 2 of treatment and

onwards. Amendment to 13 continuation scripts in Year 2 of treatment onwards resulted in an estimated cost to the PBS of also less than $10 million per year in Year 5.

Recommendation and Reasons:
The PBAC recommended the listing of certolizumab on the PBS as an Authority required benefit for the treatment of rheumatoid arthritis in combination with methotrexate and as monotherapy where there is a contraindication or intolerance to methotrexate on a cost minimisation basis with adalimumab on drug costs alone. The equi-effective doses are certolizumab 400 mg at weeks 0, 2, 4 followed by 200 mg every 2 weeks or 400 mg every 4 weeks and adalimumab 40 mg administered every 2 weeks.

The submission presented an indirect comparison via placebo of certolizumab and adalimumab with and without methotrexate. The PBAC noted that the only certolizumab trials that were consistent with the TGA recommended doses were trials CDP870-027 and CDP870-050 which used a 400 mg loading doses at 0, 2 and 4 weeks followed by 200 mg every two weeks and where methotrexate was given concomitantly. On the totality of the evidence, the PBAC accepted that certolizumab plus methotrexate and as monotherapy was non inferior to adalimumab in terms of comparative effectiveness at the recommended TGA dose (400 mg loading dose with a 200 mg biweekly or 400 mg four weekly maintenance dose).

The PBAC noted that while no formal indirect comparisons of adverse event data for certolizumab and adalimumab was presented in the submission, the sponsor in its pre-PBAC advice provided an indirect comparison of key safety outcomes based on absolute numbers which indicated that there was no evidence of differences in the pattern and incidence of adverse events in rheumatoid arthritis patients treated with certolizumab to currently listed anti TNF agents.

The PBAC considered that the requested restriction and interchangeability criteria for certolizumab should be identical to those of adalimumab but would also need to incorporate the changes recommended at the December 2009 special PBAC meeting for all PBS listed bDMARDs for rheumatoid arthritis.

Recommendation:
CERTOLIZUMAB PEGOL, injection, 200 mg in 1 mL single use pre-filled syringe

Restriction:	Authority Required To be finalised
Maximum quantity:	2
Repeats:	2 (Initiation), 5 (continuing)

13. Context for Decision
The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

UCB welcomes the decision of the PBAC to make Cimzia (certolizumab pegol) available as a treatment option for patients living with rheumatoid arthritis.