NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Multiple Technology Appraisal (MTA)

Certolizumab pegol for the treatment of rheumatoid arthritis that has previously been treated with conventional disease-modifying anti-rheumatic drugs

Executive Summary

- This submission demonstrates that certolizumab pegol is dominant over all comparators other than infliximab (incremental cost-effectiveness ratio [ICER] of £2,243 per quality-adjusted life year [QALY] gained) for RA patients with severe disease activity who have previously been treated with conventional DMARDs.
- Certolizumab pegol is a clinically effective treatment with an acceptable risk-benefit ratio for RA patients with moderate or severe disease activity.

Background

Rheumatoid arthritis (RA) is a chronic, systemic, disabling, auto-immune, inflammatory disorder with a high patient and economic burden.[3, 4] RA is one of the most common auto-immune diseases, with the prevalence in England estimated to be approximately 0.8%.[5] Approximately 580,000 people in the UK have been estimated to have RA, with approximately 26,000 new cases diagnosed each year.[6] Annual healthcare costs to the NHS due to RA are estimated to be £560 million, and costs to the economy due to sick-leave and work-related disability were estimated at £1.8 billion.[6] The overall cost of productivity losses due to RA to the UK economy is almost £8 billion per year.[3] Typically, the burden of RA increases with greater disease activity, as this has a larger disabling effect hindering productivity. Whilst patients exhibiting moderate disease activity (MDA) may have fewer involved joints, MDA is still associated with a significant burden for the patient and society, demonstrated by reduced quality of life, reduced productivity, increased risk of comorbidities and increased costs when compared to remission.[7-12]

Severe disease activity is defined as a DAS28 score of >5.1 and is used interchangeably in this submission with the term high disease activity (HDA). MDA is defined as a DAS28 score of >3.2 and ≤5.1.

MDA is associated with a substantial burden of disease, such as pain, fatigue, loss of physical function, and impaired quality of life and work productivity. Patients who have MDA may have more manageable signs and symptoms of disease, but can nonetheless be at high risk for rapid radiographic progression leading to permanent structural damage and loss of function. For these reasons, treatment guidelines (including those from the British Society of Rheumatology) stipulate the importance of minimising the level of disease activity, with remission or LDA as the target of therapy. Importantly, this includes the use of anti-TNFs in patients with MDA. Registry and clinical trial data has demonstrated the clear treatment benefit of anti-TNF therapy in the MDA population.[13,14, 15] As such, patients exhibiting MDA represent a clinically and economically relevant population in the spectrum of RA disease who may benefit from anti-TNF therapy.

Currently in the UK, as per NICE guidelines, treatment with biologics is not initiated unless patients have severe disease activity (DAS28 >5.1).[16] Emery et al. (2009) have described stark variability in the framework for the initiation of anti-TNFs across Europe.[17] In general, it was found that TNF inhibition could be started from 3-6 months following a confirmed diagnosis of RA and an inadequate response to DMARD therapy. However, in the UK, a minimum of 1 year is required between diagnosis and anti-TNF therapy (except in cases of DMARD intolerance).[17] Therefore there remains a clinical unmet need in the treatment of RA patients with MDA in the UK.

The Technology

Certolizumab pegol (CZP; CIMZIA®, UCB) is a PEGylated, Fc-free, anti-TNF for the treatment of RA. It has a high affinity, neutralising potency, and specificity for human TNF-α, a key pro-inflammatory cytokine with a central role in inflammatory processes. CZP is the only PEGylated anti-TNF approved for the treatment of RA.

CZP, in combination with MTX, is indicated in Europe for the treatment of moderate-to-severe, active RA in adult patients where the response to DMARDs, including MTX, has been inadequate. CZP can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is

inappropriate. CZP 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.[1]

CZP is provided in a specially-designed patient friendly, pre-filled syringe developed in cooperation with clinical experts and manufactured by OXO Goodgrips®. This syringe has been associated with significant administration and biomechanical advantages.[18] Compared with other anti-TNF agents, CZP has demonstrated consistently low levels of injection site reactions (including reduced injection site pain) that are commonly associated with subcutaneous administration.[1,19, 20] The recommended starting dose for adults with active RA is 400 mg (as 2 injections of 200 mg each on one day) at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every 2 weeks. In accordance with NICE guidance, treatment may be continued for as long as an adequate response (as measured by an improvement of ≥1.2 in disease activity score) is maintained.

The acquisition cost will be £357.50 per 200 mg syringe (excluding VAT). CZP will be provided within a patient access scheme in which treatment is provided without any charge for the first 12 weeks.

In the UK, according to NICE guidelines, CZP provides a treatment option after inadequate response to conventional DMARDs for the treatment of severe active RA, alongside other biological DMARDs including adalimumab, infliximab, etanercept, golimumab and tocilizumab.[2, 21-23]

Clinical Efficacy of CZP

To date, the clinical evidence for CZP is provided in ten placebo-controlled, randomised trials (RCTs), all of which have provided consistent results, and have supported the rapid onset of action of CZP.

Clinical Efficacy of CZP in a Severe Disease Activity Population

In the pivotal RAPID 1 (n=982) and RAPID 2 (n=619) trials, in which patients were inadequate responders to MTX, ACR20/50/70 responses in both the CZP 200 mg and 400 mg groups were clinically and statistically significantly greater than in the placebo groups (P≤0.01 for all outcomes).[24, 25] CZP was shown to have a rapid onset of effect and the difference between CZP and placebo in ACR20 response was significant at all time-points from week 1 onwards.[55, 56] In the RAPID 1 and RAPID 2 trials, CZP + MTX inhibited the progression of structural damage to a greater extent than placebo + MTX at 24 weeks.[55, 56] In RAPID 1 a significantly greater proportion of CZP patients achieved clinically meaningful improvements in health-related quality of life.[27] Relief from pain and fatigue was significantly reduced in the CZP groups of the RAPID 1 trial compared to placebo as early as week 1, and this relief was sustained throughout the study.[24,28] Additionally, CZP + MTX improved productivity both outside and within the home, and resulted in more participation in social activities in both RAPID trials.[29] Three studies conducted in an Asian population, J-RAPID (n=316), HIKARI (n=230) and the Korean study (n=121), demonstrated consistent findings with those of the RAPID trials.[30, 31, 32]

The FAST4WARD trial (n=220) investigated the efficacy and safety of CZP 400 mg Q4W as monotherapy in patients who were inadequate responders to at least one prior DMARD. In this study, the onset of action was rapid, and the difference between CZP monotherapy and placebo in ACR20 response was significant at all time-points from week 1 onwards (P≤0.01).[33] The ACR20 response in the CZP group was clinically and statistically significantly greater than in the placebo groups. In the FAST4WARD monotherapy trial, patients treated with CZP also experienced rapid, sustained, clinically meaningful and statistically significant improvements in physical function.[33] These results were consistent with those from the REALISTIC trial (n=1,063), which investigated the safety and efficacy of CZP in a broad population of RA patients, including those with prior anti-TNF use and a range of concomitant conventional DMARDs (cDMARDs).[34]

Clinical Efficacy of CZP in a Moderate Disease Activity Population

The efficacy of CZP has been demonstrated in patients with moderate disease activity in the CERTAIN trial (n=194), in which 91.2% of patients had MDA as based on DAS28 score at baseline.[14] In this trial, over twice as many CZP-treated patients achieved a state of DAS28 remission or low disease activity

(LDA) when compared with placebo-treated patients at week 24.[14] CZP was also associated with the prevention of disease worsening measured through DAS28, clinical disease activity index (CDAI) and simplified disease activity index (SDAI) responses.[14] The data from the CERTAIN study demonstrate not only the effectiveness of CZP in reducing disease activity in patients with MDA, but also that CZP is effective at halting disease worsening in patients with moderate disease activity.[35] The results from CERTAIN show that the addition of CZP to conventional DMARDs in patients with moderate disease activity is associated with increased rates of remission and LDA and improvements in work productivity, physical function and quality of life. Taken alongside the level of functional and work capacity impairment experienced by patients with persistent MDA,[9] and the low likelihood of these patients achieving LDA or remission with cDMARD treatment alone,[36] the data suggest that RA patients with moderate disease activity are a relevant population to treat with CZP.

The results from the trials presented in this submission demonstrate that patients treated with CZP experience rapid and sustained improvements to their emotional and physical well-being.

Rapid Response and Predictability of Response with CZP

According to the European League Against Rheumatism (EULAR) treat to target (T2T) guidelines, remission or LDA are the minimal aspired goals of RA therapy.[37] Until the desired target is achieved, the guidelines recommend that therapy be assessed at least every 3 to 6 months, and that measures of disease activity must be documented regularly to enable appropriate therapeutic adaptation.[37] This enables non-responding patients to move to an alternative therapy, potentially reducing the risk of continued disease activity resulting from ineffective treatment.

CZP has demonstrated a consistently rapid response in all RCTs presented in this submission. Furthermore, it has been demonstrated that an early response is associated with better long-term outcomes and that lack of response by week 12 is associated with a low probability of reaching the target disease activity state. Post-hoc analyses of long-term data from RAPID 1 demonstrated that rapid attainment of clinical benefit (within 12 weeks) in patients with RA receiving CZP treatment was associated with improved long-term outcomes, with earlier clinical benefit being associated with better control of disease activity.[24] Conversely, failure to achieve improvement in DAS28 within the first 12 weeks of CZP therapy was predictive of a low probability of achieving LDA at 1 year.[38] In the REALISTIC study, for any given threshold in DAS28 or swollen joint count (SJC), the failure to respond by a later time-point was associated with a lower chance of achieving LDA at week 28.[39] This allows treatment decisions regarding CZP use to be taken at an early time-point, which represents a step-change in the management of RA. To allow an early decision on the effectiveness of CZP therapy to be taken (see Section **Error! Reference source not found.**), UCB has developed an innovative patient access scheme in which treatment for patients is provided to the NHS free of charge for the first 12 weeks.

Mixed Treatment Comparison

A mixed treatment comparison (MTC) was performed to assess the relative efficacy of CZP and the comparators listed in the scope for patients with severe disease activity. No MTC was possible for the moderate disease activity population. Only trials that assessed licensed doses in patients who had previously failed conventional DMARDs were included in the MTC.

For the population with severe disease activity, the MTC showed that CZP in combination with MTX and as monotherapy was favourable to comparators in the majority of cases (relative risk compared to CZP of greater than 1) for ACR20/50/70, DAS28 remission and DAS28 low disease activity. Several cases reached statistical significance: at 24 weeks, CZP plus MTX was found to have a statistically significant benefit in ACR20 response compared to abatacept plus MTX, golimumab plus MTX, infliximab plus MTX and tofacitinib 5 mg bi-daily plus MTX. No comparator was found to be significantly more effective than CZP combination therapy or monotherapy for any outcome investigated.

Safety

The safety of CZP in RA has been comprehensively evaluated based on 10 completed RCTs and any associated open-label extension. In the longer-term safety analysis for CZP in RA, no new safety signals have emerged, and the adverse event profile is in line with that previously reported and with other biologics, including anti-TNFs.[23,27]

Cost-Effectiveness

A cost-effectiveness model was developed with a Markov (cohort health state transition) structure, in which patients with an inadequate response to MTX were evaluated from the start of treatment with CZP or a comparator. For the severe disease activity population, the relative efficacy of treatment was based on ACR response, whereas for the moderate disease activity population EULAR response was used, and utilities and costs were assigned accordingly.

For the severe disease activity population, CZP + MTX was cost-effective against infliximab + MTX at an ICER of £2,243 per QALY gained, and dominated all other comparator combination therapies. Probabilistic sensitivity analyses demonstrated that for a willingness-to-pay threshold of over £10,000 per QALY gained, the probability that CZP + MTX is the optimal treatment was over 70% in all cases. As monotherapy in the severe disease activity population, CZP dominated adalimumab and tocilizumab, and was less costly with similar QALYs compared to etanercept.

In the moderate disease activity population, CZP + conventional DMARD therapy was found to have a base case ICER of £55,916 per QALY gained over placebo + conventional DMARDs. CZP + MTX was found to have a base case ICER compared to placebo + MTX of £73,163 per QALY gained.

Budget Impact

For the severe disease activity population, it was estimated that the recommendation of biological therapy would result in a budget impact of £229,416,606 in 2013, rising to £236,985,541 in 2017. For the scenario considered in which there is increased CZP use compared to the base case, the budget impact fell, due to the displacement of more expensive treatments.

To analyse the effect of recommendation of biological therapy in the moderate disease activity population, the scenarios analysed were those where the current use of biological therapy in RA patients (6%) would increase to 8%, 11% or 12%, based on comparison with European countries with a lower DAS28 threshold for biological therapy.[40] These scenarios resulted in an incremental budget impact of £64,261,277, £159,716,403 and £191,284,967 respectively in 2017. However, it is likely that this budget impact will be largely outweighed by productivity gains within a societal context.