Executive Summary

Rheumatoid arthritis (RA) is a progressive, destructive, lifelong condition associated with significant co-morbidity. RA causes reductions in life expectancy and quality of life, and represents a high economic burden

RA is a progressive, destructive, lifelong condition characterised by inflammation of synovial membranes and widespread synovial joint involvement (1). Multiple regions, particularly hands and feet, are commonly affected by deformity and progressive disability is a consequence (2). RA is associated with long-term morbidity (1), increased mortality compared with the general population (1, 3) and has a severe impact on quality of life (QoL).

Approximately 580,000 people in England are affected by RA. Prevalence in females is higher than in men (1.16% females, 0.44% males (4)), with typical age of onset between 40 to 70 years, peaking in the fifth decade of life (3). The economic burden of RA is substantial with annual direct (healthcare) and indirect (sick-leave and work-related disability) UK costs estimated at £560 million and £1.8 billion a year, respectively (5).

No cure currently exists for RA. Consequently, the focus of treatment is to achieve remission or low disease activity as soon as possible (6). Further targets include controlling pain and inflammation whilst minimising loss of function, joint damage and disability (7), and decreasing mortality (8). In order to meet the main targets in RA recent data suggest that early and aggressive approaches to treatment are required (9). Regardless of the stage of RA, most patient populations experience a clinical benefit from treatment.

There is a role for biological DMARD treatment in a variety of RA populations

EULAR guidelines recommend treatment with conventional disease modifying antirheumatic drugs (cDMARDs) (including methotrexate [MTX]) once diagnosed with RA (6). However, limitations with respect to both efficacy and safety of cDMARDs mean that a clear, unmet need exists for alternative therapies that reduce joint damage.

The advent of biological DMARDs (bDMARDs), such as tumour necrosis factor (TNF) inhibitors, has improved patient outcomes in those patients who have an inadequate response (IR) to cDMARDs. TNF inhibitors suppress and control the inflammatory action of RA by targeting the cytokine TNF-α, preventing progression and enabling disease remission (10). The use of bDMARDs, and specifically TNF-inhibitors, has been described as a significant advance in the management of RA (11-14) with remission an increasingly realistic target (12). TNF-inhibitors are an effective therapy both in patients with high and moderate disease activity (12).

Within this submission evidence is presented for three RA patient populations of interest: Severe DMARD-IR[1] (DAS28 >5.1), Severe naïve[2] (DAS 28>5.1), and Moderate to Severe DMARD-IR (DAS28>3.2 and ≤5.1).

The benefits of bDMARDs (including TNF-inhibitors) in patients with severe DMARD-IR RA are well established and previous NICE technology appraisals (e.g. TA130, TA186, TA225 and TA247) endorse their use in this population (15-18). Monotherapy with some bDMARDs

[1]adults who have failed to respond to at least two conventional DMARDs including MTX
[2]adults who have not previously received cDMARDs (i.e. DMARD-naïve)

such as etanercept (ETN) is also recommended by NICE for use in patients with severe RA for whom MTX treatment is not appropriate (15).

EULAR guidelines also indicate that first-line bDMARD+MTX combination therapy should also be considered in patients with very active disease or early structural damage (6) (e.g. the Severe Naïve population).

However, within the UK, patients with moderately active RA (DAS28 >3.2 to ≤5.1) despite treatment with cDMARDs typically remain on MTX in accordance with current NICE guidance as the use of TNF-inhibitors is restricted to those with high DAS28 (12, 19). Therefore, Moderate to Severe DMARD-IR patients in England and Wales have limited treatment choices. This is despite, the fact that clinical data suggest disease progression is a risk in patients with persistent Moderate to Severe RA despite MTX treatment (19-21) demonstrating an unmet need in this population.

The British Society of Rheumatology (BSR) Biological Group has suggested that patients with persistent DAS28 levels of between 3.2 and 5.1 (i.e. Moderate to Severe RA) have outcomes that are not dissimilar to those with persistent levels >5.1 (i.e. severe RA) (14). Furthermore the BSR states that some patients may not strictly fulfil current NICE criteria for biologic therapies, but nevertheless have serious potentially progressive, disabling or life-shortening conditions (14) and may benefit from receiving biologics (22).

EULAR guidelines indicate that subgroups of Moderate to Severe RA patients (i.e. those with poor prognostic factors) would benefit from bDMARDs (6). The use of baseline predictors to assess the risk of progression (such as rheumatoid factor [RF] positivity and C-reactive protein [CRP] levels) (19) may help clinicians to manage patients in the Moderate to Severe active RA population according to the current treatment guidelines and to effectively achieve remission (23) whilst minimising cost. Achieving remission in the Moderate to Severe RA population has been shown to inhibit radiographic progression irrespective of disease activity (24). Patients with a DAS28 <5.1 have a disease activity response that is as good as, if not better than, patients with a DAS28 >5.1 (14). In addition, patients treated with a DAS28 <5.1 have equally as good an improvement in HAQ as those with a DAS28 >5.1, suggesting that this is an effective use of bDMARDs such as TNF-inhibitors (14).

Delaying the onset of disability, minimising impaired function and potential reductions in the need for joint surgery may bring economic benefits in patients with severe RA (DMARD-IR and naïve) and Moderate to Severe RA.

Etanercept is an innovative, targeted therapy for a variety of patient populations with RA

Etanercept (ETN) is a TNF inhibitor that has been extensively studied in patients with RA for over 15 years. By blocking TNF, ETN reduces inflammation and other signs and symptoms of RA. It has proven efficacy when given alone or in combination with MTX in patients who have failed DMARD treatment (i.e. have established disease), and in DMARD naïve patients.

ETN, alone or in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function (25). In the assessment group report for TA130, ETN (alone or in combination with cDMARDs) was effective in reducing the signs and sympotms of RA in established disease (26). ETN was also more effective than MTX in slowing radiographic joint damage in MTX-naïve patients with short disease duration (< 3 years) (26). Furthermore, ETN was marginally more

effective and better tolerated than MTX (the ‘gold standard’ in RA treatment) in MTX-naïve patients with short disease duration (<3 years) and in patients with longer disease durations who had not failed MTX treatment (26).

ETN has an advantage over intravenously administered TNF inhibitors in that it can be self-administered via a subcutaneous injection and therefore patients have more control over their therapy and can be treated at home.

NICE currently recommends ETN:

- In combination with MTX for the treatment of severe active RA (as measured by disease activity score [DAS28] > 5.1) in adults who have failed to respond to at least two cDMARDs including MTX, (Severe DMARD-IR) (TA130) (15).
- Where a patient is intolerant of MTX or where MTX is considered to be inappropriate, etanercept may be given as monotherapy (TA130) (15).
- In combination with MTX or as a monotherapy in adults with severe active RA who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor where rituximab is contraindicated or withdrawn or cannot be given because MTX is contraindicated or withdrawn (TA195) (27) (not considered as part of this appraisal).

Although the use of ETN in severe DMARD-IR RA is well established, it provides clinical benefit in patients with RA of varying disease activity. ETN is suitable for use in patients with moderate RA (as per the licensed indication), particularly those who are at high risk of radiographic progression and also for patients with severe RA who have not previously received cDMARDs (Severe Naïve [DAS28 >5.1]).

Etanercept significantly improves the signs and symptoms of Severe DMARD-IR RA when compared with cDMARDs

The efficacy of ETN as a combination therapy (with MTX) and as a monotherapy has been clearly demonstrated in clinical trials and via registry data:

- Combination therapy with ETN+MTX is significantly more efficacious compared with MTX monotherapy with regards to key clinical outcomes such as American College of Rheumatology (ACR) criteria, EULAR responses, tender/swollen joint counts, and patient reported outcomes (28-31).
- ETN monotherapy is significantly more efficacious than placebo with regards to ACR20/50/70 responses and tender/swollen joint counts (32, 33).
- Data from the BSRBR indicate that patients treated with ETN experienced reduced disability, disease activity and higher rates of long-term remission than those treated with cDMARDs (34).

Etanercept is differentiated from other DMARDs in Severe DMARD-IR RA

Biological DMARDs are the focus of treatment in Severe DMARD-IR RA and ETN, adalimumab (ADA), and infliximab (INF) have previously been jointly assessed and recommended in NICE TA130 (15).

It is proposed within this submission that ETN has a unique mode of action. Clear differentiation in the efficacy of ETN has been shown versus ADA, INF and ABT and therefore ETN should be considered distinct from other bDMARDs.

- Although ETN, ADA, and INF are all TNF-inhibitors, key differences exist in their molecular structures: ETN is a recombinant human TNF-α-receptor fusion protein whereas ADA and INF are monoclonal antibodies.
- Unlike monoclonal antibodies such as INF and ADA, ETN demonstrates sustained efficacy with predictable dosing (35).
- The absence of clinically significant immunogenicity attributable to ETN constitutes a key differentiating factor and may be associated with the higher drug survival that has been reported for ETN in comparison with INF or ADA (36-39).
- A published network meta-analysis (NMA) by Orme et al, 2012 has demonstrated that with regards to improving ACR20/50/70 (recognised outcomes in RA clinical trials) ETN+MTX is significantly better than ADA and INF (all treatments in combination with cDMARDs) (40).
- An update to the Orme et al, 2012 NMA, included in this submission demonstrated that ETN is significantly better than ADA and INF for ACR20/50/70 outcomes. Furthermore, ETN was shown to be significantly better than abatacept (ABT) intravenous with regards to ACR20/50/70 outcomes and ABT subcutaneous for ACR20/70.
- Registry data suggests that time on treatment/drug survival with ETN is longer than with INF or ADA (41-44) and is potentially a differentiating factor between these TNF-inhibitors.

Etanercept demonstrates clinical efficacy in Moderate to Severe RA

- The efficacy of ETN+MTX has been clearly demonstrated in a truly moderate RA population (PRESERVE) – limited data are available for other bDMARDs in this population.
- In moderate patients who have reached low disease activity after initial ETN+MTX combination therapy (PRESERVE), ETN+MTX more effectively maintained low disease activity than MTX alone (45).
- A naïve comparison between CERTAIN (CZP) and PRESERVE Period 1 (ETN) suggests that ETN has greater efficacy with regards to improvements in ACR20/50/70, DAS28 remission, and change from baseline HAQ. However, such evidence should be viewed with caution as the methodology of the studies varies to a great extent.

There is a clinical benefit in the earlier use of etanercept in patients with Severe Naïve RA

- The early use of ETN (in combination with MTX) induces remission and halts progression of joint damage in a Severe Naïve RA
    - COMET demonstrated that remission is an achievable goal with ETN+MTX compared with MTX alone – with consistent improvements observed for clinical disease, radiographic and functional status (46-51)
    - PRIZE demonstrated that ETN+MTX combination therapy resulted in significant improvements of clinical, functional, and health outcome measures, with minimal radiographic progression (52)

Etanercept has a trusted long-term safety and tolerability profile established through over 3 million patient-years of experience

The safety and tolerability profile of ETN has been clearly demonstrated in an extensive clinical trial programme and serious infections and withdrawals have been assessed via NMA:

- As of 16th August 2012, 18,081 patients had been exposed to ETN in trials for the approved indications (RA, polyarticular juvenile idiopathic arthritis [JIA], extended oligoarticular JIA, enthesitis-related arthritis, paediatric and adult psoriatic arthritis, ankylosing spondylitis, adult plaque psoriasis, and paediatric plaque psoriasis) – including 15,071 subject-years in 7830 subjects with RA (53).
- ETN has generally been well-tolerated throughout key trials, with both ETN 25 mg BIW and ETN 50 mg OW dosage regimens showing similar safety profiles (54).
- The most recent ETN studies and long term follow up of real world and study cohorts have not changed the risk benefit profile of ETN.
- In one of the longest prospective studies of TNF inhibitor therapy to date (some patients received >10 years of treatment) ETN had an acceptable safety profile both in early and longstanding RA patients and the risk/benefit ratio of continuous long-term ETN treatment was favourable (55).
- Analyses of the BSRBR ETN dataset have demonstrated that there was no evidence of adverse outcome from long-term exposure to ETN and ETN therapy was not associated with any overall increased risk of serious infection, malignancy, cardiovascular events or death when compared with a DMARD reference group (34, 56).
- ETN is at least comparable with other bDMARDs with regards to key safety and tolerability outcomes
- BSRBR data shows ETN treatment has lower tuberculosis (TB) rates than either ADA or INF
- BSRBR data shows ETN treatment has reduced lower respiratory tract infection (LRTI) rates than either ADA or INF
- NMA demonstrates that ETN has a safety and tolerability profile at least comparable with other bDMARDs with respect to withdrawals due to adverse events (AEs), number of patients with serious infections, and rate of serious infections.
- The acceptable safety profile of ETN has been well established in an extensive clinical programme and through real-world experience in a variety of patient populations with RA.

Etanercept is a cost-effective treatment option for the NHS

A discrete event simulation model demonstrated the following:

- In the Severe DMARD-IR combination therapy population, a strategy headed by ETN was compared with strategies headed by all other bDMARDs and cDMARDs defined in the NICE scope

    - Based on an incremental analysis, the strategy headed by ETN had an ICER of £20,520 vs a cDMARD strategy
    - All other strategies were extendedly or strictly dominated by the strategy headed by ETN

- In the Severe DMARD-IR monotherapy population, a strategy headed by ETN was compared with strategies headed by ADA, TOC (with alternative second therapies [ETN or ADA]), and cDMARDs
    - Based on an incremental analysis, the strategy headed by ETN had an ICER of £26,335 vs a cDMARD strategy
    - All other strategies were extendedly or strictly dominated by the strategy headed by ETN

- In the Moderate to Severe population, a strategy headed by ETN was compared with a strategy headed by cDMARDs
    - Based on an incremental analysis, the strategy headed by ETN had an ICER of £24,727 vs a cDMARD strategy

- In the Severe Naïve population, a strategy headed by ETN was compared with a strategies headed by cDMARDs and combination cDMARDs
    - Based on an incremental analysis, the strategy headed by ETN had an ICER of £34,373 vs a combination cDMARD strategy
    - All other strategies were extendedly or strictly dominated by the strategy headed by ETN

- The ICERs above are presented from the perpective of the NHS and PSS, however, significant cost savings are likely to be realised from using bDMARDs instead of cDMARDs if a societal perspective is taken.

Budget Implications for the NHS

The total number of patients eligible for the bDMARDs based on the incidence and prevalence estimates in the populations of interest (Severe DMARD-IR, Moderate to Severe, and Severe Naïve RA) is estimated at 59,764, 60,254 and 60,735 for 2014, 2015 and 2016, respectively.

- Results suggest that the likely budget impact of the new populations of interest (Moderate to Severe and Severe Naïve RA) is likely to be smaller than that of Severe DMARD-IR RA
    - In Moderate to Severe and Severe Naïve RA the total prevalence and incidence of patients eligible for bDMARDs will be 20,125, 20,290 and 20,458 for 2014, 2015, and 2016, respectively.

Conclusion

The advent of bDMARDs, such as TNF inhibitors, has improved outcomes for patients with RA and this submission demonstrates that there is a clear role for the use of bDMARDs in disease of varying severity.

Strong evidence derived from clinical trials, registries, observational studies and NMA support the efficacy and safety profile of ETN in patients with varying disease activity according to DAS28 (Severe DMARD-IR [DAS28 >5.1], Moderate to Severe [DAS28 >3.2 and ≤5.1], and Severe Naïve [DAS28 >5.1]).

- ETN is a TNF inhibitor that has been extensively studied in patients with RA for over 15 years.
- The efficacy of ETN has been clearly demonstrated both in patients who have failed DMARD treatment (i.e. have established disease), and in DMARD naïve patients.
- ETN consistently improves the signs and symptoms of RA when used as combination or monotherapy in Severe DMARD-IR and Severe Naïve populations and as combination therapy in Moderate to Severe RA versus cDMARDs.
- Clinical trial and registry data supports the use of ETN for inducing and maintaining clinical remission of RA in patients with varying disease activity.
- ETN is clearly differentiated from other bDMARDs with regards to improved efficacy (ACR outcomes) and time on treatment data in a Severe DMARD-IR population.
    - ETN in combination with MTX and as a monotherapy significantly improves the signs and symptoms of RA in patients who have had an inadequate response to ≥1 DMARD.
    - The absence of clinically significant immunogenicity attributable to ETN constitutes a key differentiating factor and may be associated with the higher drug survival that has been reported for ETN in comparison with INF or ADA. (36-39).
- In a truly moderate population of patients with established active RA, ETN demonstrates statistical superiority consistently across multiple clinical, health outcomes assessments, and radiographic endpoints compared with MTX.
- The early use of ETN (in combination with MTX) induces remission and halts progression of joint damage in Severe Naïve RA.
- ETN is well-tolerated with an acceptable safety profile as demonstrated via 15,071 subject-years in 7,830 subjects with RA
    - The most recent ETN studies have added no new safety concerns to those noted previously.
- The economic evaluation presented in this submission demonstrates that a treatment strategy headed by ETN is cost-effective for patients with Severe DMARD-IR (combination and monotherapy) and Moderate to Severe RA.
- Although a treatment strategy headed by ETN slightly exceeds the £30,000 cost-effectiveness threshold in a Severe Naïve population, this approach is considered the most cost-effective of the bDMARD headed strategies explored.

ETN offers sustained and predictable clinical efficacy with a trusted long-term safety and tolerability profile established through over 3 million patient-years of experience. Delaying the onset of disability, minimising impaired function and a potential reduction in the need for

joint surgery may lessen the economic burden associated with the management of patients with severe RA (DMARD-IR and naïve) and moderate RA.