Executive Summary

Background

With nearly 400,000 patients affected by Rheumatoid Arthritis (RA) within England and Wales, early initiation of therapy with biologic disease-modifying antirheumatic drugs (biologic DMARDs), including tumour necrosis factor α (TNFα) inhibitors is a critical component in the pharmacological management of this chronic, debilitating condition. Clinical evidence suggests that patients with RA respond variably to biologic DMARDs with up to 70% responding within 6 months. Patients with RA will benefit from proven treatment options which address the challenges throughout the treatment pathway in DMARD experienced and biologic DMARD experienced patient populations.

In the last 10 years, the emergence of TNFα inhibitors and more recently the increase in choice of biologic DMARDs have had a considerable effect on the treatment of RA. There is agreement between patient representatives, the British Society for Rheumatology (BSR), and manufacturers that the positive recommendations from the National institute for Health and Clinical Excellence (NICE) and the Scottish Medicines Consortium (SMC) have helped to change thousands of lives for the better.

The BSR and British Health Professionals in Rheumatology (BHPR) published guidelines on the eligibility criteria for the first biologic therapy in 2010. This was the first major update since the first guidelines were produced a decade before in 2000. In these guidelines, the BSR collate and summarise a large quantity of studies to inform their recommendations; namely a reduction in the Disease Activity Score (DAS28 - a measure of the activity of the disease in patients with RA based on 28 defined joints) threshold for initiation of a biologic DMARD from 5.1 to 3.2, citing the following points as drivers for this change in clinical practice:

1. The NICE RA Management Guidelines recommend intensive use of combinations of conventional DMARDs and steroids in early active disease. A DAS28 of 5.1 is too high to identify those patients who are not showing a satisfactory response to such regimens;
2. Patients with persistent DAS28 levels of between 3.2 and 5.1 have outcomes that are not dissimilar to those with persistent levels >5.1;

3. Patients with a DAS <5.1 have a disease activity response to TNFα inhibitor therapies that is as good as, if not better than, patients with a DAS28 >5.1; and
4. An analysis of British Society for Rheumatology Biologics Registers (BSRBR) data suggests that patients treated with a DAS28 <5.1 have just as good an improvement in Health Assessment Questionnaire (HAQ) as those with a DAS28 >5.1, suggesting that this is a cost-effective use of TNFα inhibitor

MSD believes that these guidelines are fully in line with the available evidence and therefore supports their recommendations. We believe a lowering of the DAS28 threshold is an opportunity for thousands more patients to benefit from earlier and more effective treatment. The health economic modelling results support the BSR's conclusion that treating patients with a DAS28 of 3.2 with a TNFα inhibitor is as cost-effective as treating those with a higher DAS28 of 5.1.

The BSR analyses suggest that a reduction in the DAS28 threshold would result in an increased uptake of biologic DMARDs to between 8% and 12% of patients if UK clinical practice aligns to European standards. However, the level of biologic DMARD use could actually decrease by following NICE RA Management guidelines and treating active disease with combinations of conventional DMARDS and steroids closer to symptom onset.

Together with the backing of NICE guidance the BSR and BHPR guidelines could significantly change clinical practice in the UK, opening access to earlier treatment for patients with RA. The economic and clinical case has been made for the lowering of the DAS28 threshold; MSD would request NICE to reflect that in its guidance.

MSD has submitted clinical and cost-effectiveness evidence for the only intravenous (IV) infusion TNFα inhibitor, infliximab (Remicade®) to inform the appraisal of infliximab for the treatment of RA after failure of previous DMARDs within the context of this MTA review, which is considering extending the eligible population to those with moderate disease.

Infliximab has been found to have comparable efficacy and adverse event profile to the existing biologic DMARDs. With comparable acquisition costs across the biologic DMARD class, the evidence supports infliximab as a cost-effective treatment alternative

within the NICE willingness to accept threshold. The incremental cost-effectiveness ratio (ICER) of infliximab compared to previous standard care is similar to ICERs of other biologics which are currently recommended for treatment by NICE.

RA is the most common inflammatory arthritis in England and Wales associated with severe disability, premature mortality and considerable economic implications: total costs of RA in the United Kingdom (UK) are estimated to exceed £1 billion per annum.

In the treatment of RA after failure of two DMARDs (including methotrexate [MTX]), NICE has recommended the use of the biologic DMARDs certolizumab (TA186), adalimumab, etanercept, and infliximab (TA130), golimumab (TA225), and tocilizumab (TA247). NICE has also reviewed abatacept for the treatment of RA after the failure of two DMARDs, however NICE did not recommend the use of abatacept for this indication. A rapid review of abatacept is on-going at present.

Randomised controlled trial (RCT) evidence strongly supports a robust clinical and adverse event profile for infliximab, which improves the signs and symptoms of RA, slowing progression of joint damage and improving physical function.

The Technology

The key features of infliximab are presented in Table 1 as follows:

Table 1: Key Features of Infliximab

Approved name	Infliximab
Brand name	Remicade®
Marketing status	Marketing authorisation for RA granted May 1999
Pharmacological action	Chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and trans-membrane forms of TNFα but not to lymphotoxin α (TNFβ)
Formulation	Powder for concentrate for solution for infusion
Dosing frequency	3 mg/kg given as an IV infusion followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter Remicade® must be given concomitantly with MTX
Average length of a course of treatment	In accordance with NICE Guidelines, treatment should continue as long as an adequate response (an improvement of ≥1.2 in DAS) is maintained. Available data suggest that the 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 or after dose adjustment
Average interval between courses of treatments	Continuous treatment for at least 12 weeks and then until no response or loss of response
Indications	*Rheumatoid Arthritis (RA)*: Remicade®, in combination with methotrexate, is indicated for the

	reduction of signs and symptoms as well as the improvement in physical function in: • adult patients with active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate • adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated *Psoriatic arthritis (PsA):* Remicade® is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate Remicade® should be administered: • in combination with methotrexate • or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated *Ankylosing spondylitis (AS):* Remicade® is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy *Adult Crohn's Disease (CD):* Remicade® is indicated for: • treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contra-indications for such therapies • treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy) *Paediatric Crohn's Disease (pCD):* Remicade® is indicated for treatment of severe, active Crohn's disease, in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies Remicade® has been studied only in combination with conventional immunosuppressive therapy *Adult Ulcerative Colitis (UC):* Remicade® is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies *Paediatric Ulcerative Colitis (pUC):* Remicade® is indicated for treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, who have had an

	inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies *Psoriasis (PsO):* Remicade® is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate, or psoralen combined with ultraviolet A

Randomised trials have shown abatacept, adalimumab, certolizumab, etanercept, infliximab, tocilizumab, and golimumab to be effective in the treatment of RA. The advantages that infliximab provides over the other existing treatment options are:

- Intravenous administration of Remicade® allows high serum concentrations to be rapidly achieved, and therefore offers the potential for fast, complete suppression of inflammation. Remicade® can start making a difference within 48 hours for some patients; data shows that patients with RA who received Remicade® were more persistent with treatment than those receiving the subcutaneous (SC) TNFα inhibitors, adalimumab and etanercept
- IV administration of Remicade® is well accepted by patients, with some choosing the IV route for reasons of safety, rapidity, and reassurance. In particular 60% of those who preferred IV to SC stated frequency of admission as the reason and 45% stating convenience
- Optimisation programs have shown to reduce acquisition costs and wastage of Remicade® while improving patient experience. This has been achieved by reducing non-attendance, creating more effective infusion pathways, prescribing Remicade® in patients weighing less than 67 kg, vial sharing, and home infusion

Clinical Effectiveness

The safety and efficacy of infliximab has been robustly assessed with two large, randomised, controlled trials.

ATTRACT

ATTRACT was a 54 week randomised clinical trial with an extension up to 102 weeks. The primary objectives of ATTRACT were to assess the efficacy and safety profile of infliximab treatment in reducing clinical signs and symptoms of RA at 30 weeks,

preventing structural damage at 54 weeks, and improving physical function at 102 weeks.

ATTRACT met all primary endpoints, demonstrating that infliximab and MTX therapy, compared to MTX alone, results in a significant improvement at week 54 in HAQ scores with a median percentage improvement from baseline of 23% vs. 3% ($p<0.001$). Further, infliximab in combination with MTX was shown to be superior to MTX alone in improving the radiographic outcomes of patients with RA, with the infliximab-treated patients showing improvements in erosion, joint-space narrowing, and Sharp scores at 52 weeks. Infliximab (at the licensed dose of 3 mg/kg q8 weeks) in combination with MTX significantly reduced the progression of structural damage in comparison to MTX alone. In many patients treated with infliximab, progression was completely arrested, in particular, for patients with early RA (those with disease duration ≤3 years). These responses were durable and sustained through 102 weeks. Infliximab plus MTX had a significantly greater impact on all 4 physical components of the Short-Form 36 (SF-36) than did MTX alone. At 54 weeks, 30% of infliximab-treated patients rated their overall health 'excellent' or 'very good' compared to 16% with placebo ($p<0.001$). Therefore, in patients with RA, infliximab was shown to improve physical functioning and health-related quality of life (HRQL) to a greater degree than in patients treated with MTX alone.

ASPIRE

ASPIRE demonstrated that treatment of early RA with the combination of MTX and infliximab improves the signs and symptoms of disease activity, inhibits the radiographic progression of joint damage, and improves physical function better than MTX therapy alone over 1 year.

The primary and major secondary efficacy analyses were consistent in showing the superiority of the combination of MTX and infliximab over MTX alone. Patients receiving MTX-3 mg/kg infliximab and MTX-6 mg/kg infliximab achieved a significantly higher median ACR-N (38.9% and 46.7%, respectively) than those in the MTX-placebo group (26.4%) ($p<0.001$), and there were no significant differences in clinical efficacy between the 3 mg/kg and 6 mg/kg infliximab dosage groups. The mean ± SD change in the van der Heidje Modification of Sharp Total Score (vdH-S) was significantly less for

the patients receiving MTX-3 mg/kg infliximab and MTX-6 mg/kg infliximab (0.4 ± 5.8 and 0.5 ± 5.6, respectively) than for those receiving MTX alone (3.7 ± 9.6) ($p<0.001$ for each comparison). Radiographic progression of joint damage was not significantly different between the 2 infliximab dosage groups. HAQ scores improved more in the MTX-3 mg/kg infliximab and MTX-6 mg/kg infliximab groups than in the group receiving MTX alone.

The adverse event profile of the MTX–infliximab combination was similar to that observed in previous infliximab trials except for an increased risk of serious infections in the MTX–infliximab groups compared with MTX therapy alone.

Cost-Effectiveness

Systematic literature reviews and meta-analyses informed a Markov model which found infliximab 3 mg/kg to be a cost-effective treatment option for patients who demonstrate an inadequate response to DMARDs.

Table 2 presents the basecase results for all comparators within a DMARD experienced RA patient population.

Table 2: Basecase Cost-Effectiveness Results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (MTX)	Incremental analysis
methotrexate	£57,376	4.791			-	-
Infliximab	£83,887	5.845	£26,511	1.054	£25,144	£25,144
Etanercept	£84,947	5.678	£1,059	-0.167	£31,065	Dominated
Golimumab	£87,027	5.909	£2,080	0.231	£26,512	£9,010
Adalimumab	£88,750	6.117	£1,723	0.207	£23,663	£8,305
Certolizumab	£93,696	6.519	£4,946	0.403	£21,011	£12,281
Tocilizumab	£94,777	6.065	£1,080	-0.454	£29,339	Dominated
Abatacept IV	£97,346	5.710	£2,570	-0.355	£43,455	Dominated
Abatacept SC	£108,181	5.710	£10,834	0.000	£55,234	Dominated

The results indicate that infliximab is a cost-effective treatment alternative compared to standard care. The severe patient subgroup has been displayed in Table 3 below. The similarity between the results for the severe subgroup and the overall moderate to severe population supports the use of infliximab in a population with moderate disease (DAS28 ≥3.2), from an economic perspective.

Table 3: Severe Patient Subgroup Results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (MTX)	Incremental analysis
methotrexate	£58,181	4.504	-	-	-	-
Infliximab	£84,007	5.539	£25,827	1.034	£24,968	N/A

Conclusion

Robust clinical and adverse event (AE) RCT evidence supports the conclusion that patients would substantially benefit from an on-going recommendation of infliximab for the treatment of moderate to severe RA. Indirect comparisons found infliximab to be superior to the previous standard of care and there were no statistically significant differences in efficacy or adverse events to other biologic DMARDs.

As the ICER for infliximab falls under a £30,000 threshold, infliximab can be considered a cost-effective treatment option for patients with moderate to severe RA.

Infliximab is a clinically and cost-effective treatment in first line biologic treatment of RA.

Additional Considerations

Ranking by ICER

Attempts have been made in the past to 'rank' technologies where there are multiple drugs with similar efficacy that generate marginally different ICERs when modelled. Given that the data informing the network analyses is from trials of different populations at different times and in different locations this should be regarded as incorrect. At best we believe that the results from such analyses (classically with overlapping credible intervals in all or most endpoints) can support a class effect, as is the case with the network analysis used for this submission.

Abatacept

Neither formulation of abatacept can be considered a cost-effective treatment option based upon the information available to MSD (the calculated ICER in the MSD model using the list price is £34,953 for abatacept IV and £44,232 for abatacept SC). However, there is a Commercial in Confidence Patient Access Scheme (PAS) in place for abatacept, reported on the NICE website as being in the form of a simple discount and it would be reasonable to assume that the scheme would bring abatacept into line with one or more of the other biologic treatments already approved by NICE.

We have undertaken an exploratory analysis using our model to estimate the level of

discount which would be required to provide comparable cost-effectiveness for this product. In the absence of the exact discount, a 'goal seek' analysis was undertaken in the excel model to calculate the change in unit price required to achieve the median of the range of acceptable ICERs resulting from the model for other technologies (ICERS < £30,000 per QALY). For the IV formulation, a discount of 36.42% would be required to achieve comparable cost-effectiveness.

Further, if this discount on the IV formulation is carried through into the analysis for the SC formulation (for the IV loading dose only), a discount of 45.13% on the SC list price would be required achieve comparable cost-effectiveness.