Executive Summary

Rheumatoid arthritis (RA) is the most common inflammatory arthritis affecting around 1% of adults in England and Wales. RA is a chronic condition resulting in progressive disability with subsequent effects on patients' life expectancy, quality of life, ability to work or conduct usual daily activities.

Current NICE guidance recommends that adalimumab, etanercept and infliximab be made available on the NHS for the treatment of moderate to severe RA in patients who are unresponsive to conventional disease modifying anti-rheumatic drugs (DMARDs). The aim of this submission is to inform the NICE appraisal of the clinical and cost effectiveness of adalimumab, etanercept, infliximab, abatacept and rituximab for patients who have failed an anti-TNF agent for efficacy reasons.

Prior to the introduction of TNF inhibitors patients received a sequence of conventional DMARD therapies. Data for the effectiveness of conventional DMARDs in patients failing 2 or more prior therapies are extremely limited, and the data that are available from the BeSt and BROSG studies suggest that sequences of further conventional DMARDs have negligible effect in avoiding further joint erosions. Following the introduction of TNF inhibitors in 1999 compelling data have emerged that the most effective way to prevent irreversible joint damage in patients with RA is to aim for early treatment with an anti-TNF agent in combination with methotrexate. However, a proportion of patients receiving their 1st TNF inhibitor either do not respond to the therapy (primary non-response) or experience a loss of efficacy over time (secondary non-responders).

Abbott considers it is important to recommend adalimumab as a treatment option for patients failing a TNF inhibitor for the following reasons:

- Patients who have failed a TNF inhibitor have a utility on average of 0.3. These data indicate that the target patient population has a severely reduced quality of life which can only be substantially improved by biologic therapy.

- Severe RA imposes high societal costs as progressive disability leads to patients retiring early, receiving care to assist with everyday tasks and reliance on the state for financial support. Therefore, from a societal perspective effective treatment with biologic therapy will be associated with a much lower cost per QALY than if only NHS costs are included in the economic evaluation.

- It is necessary for patients to have access to a sequence of effective therapies to control the disease over their lifetime. Sequences of conventional DMARDs after failure of methotrexate have not proven effective in reducing disease progression in patients with moderate to severe disease.

- Results from the economic modelling contained in this submission indicate that adalimumab + methotrexate is a cost effective therapy option for patients that have failed a prior anti-TNF (£15,962 per QALY).

- There are a number of reasons why adalimumab may represent a more appropriate treatment option than rituximab for this patient population

    - There is uncertainty around the cost effectiveness of rituximab compared to TNF inhibitors as there are very limited data on the optimal retreatment intervals over time. An adequate response would be defined as a 1.2 point improvement in DAS28 score according to NICE guidance. At the time of loss of this response the patient should then be retreated with rituximab. It should be noted that the need to maintain a 1.2 DAS28 reduction is not included in the current NICE guidance for rituximab. The mean time to retreatment in the clinical studies of rituximab does not necessarily equate to the mean retreatment interval if a maintenance rule requiring a 1.2 point DAS28 improvement for rituximab therapy in clinical practice were to be applied. The cost effectiveness of rituximab will worsen if patients require more frequent

retreatment intervals than observed in the clinical trial where no criteria for maintenance of DAS28 response were required.

- Around 20-30% of patients with RA have seronegative disease. These patients have a lower response to rituximab whereas seronegative status does not affect the response to anti-TNF treatment.

- Patients who are intolerant of methotrexate or in whom it is contraindicated could benefit from receiving adalimumab monotherapy. Rituximab is only licensed for treatment in combination with methotrexate. Around half of anti-TNF switch patients in the BSRBR are not on methotrexate therapy.

- Modelling of treatment sequences contained in this submission indicates that reserving rituximab for use after patients have failed anti-TNF therapy is a cost effective therapy option which maximises the QALY gain over the lifetime of patients.

- Given the uncertainty over the long term safety of giving TNF inhibitors after rituximab therapy it would appear sensible to allow clinicians and patients the option of a TNF inhibitor rather than rituximab.

- Adalimumab is available as an auto-injector pen which can be administered at home. Patients may prefer this method of administration rather than a lengthy intravenous infusion of rituximab in a hospital setting.

In conclusion, there is a wealth of clinical evidence that indicates that patients receiving TNF inhibitor after failure of a prior anti-TNF for efficacy reasons receive a significant clinical benefit and improvement in their quality of life. Modelling developed for this submission indicates that sequential use of anti-TNF treatment is a cost effective use of NHS resources and will help prevent disability in patients with severe RA. As anti-TNF treatment is initiated earlier in patients with RA both in terms of disease duration and number of previous DMARDs failed, the magnitude of treatment improvements achievable with sequential therapy of these agents is likely to increase over time.