BRISTOL-MYERS SQUIBB PHARMACEUTICALS LTD

ABATACEPT (ORENCIA®)
FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

MULTIPLE TECHNOLOGY APPRAISAL
SUBMISSION TO THE NATIONAL
INSTITUTE FOR HEALTH & CLINICAL EXCELLENCE

10TH AUGUST 2009

Academic in Confidence information is underlined and highlighted e.g.
Orencia

Executive Summary

Clinical Context

Rheumatoid arthritis (RA) is a chronic and progressive systemic autoimmune disorder characterised by inflammation and swelling of synovial joints leading to joint deformity, functional impairment, pain, fatigue, and ultimately, disability. It affects approximately 400,000 people in England and Wales. RA patients have a reduced quality of life (reported as poor as patients with congestive heart failure or advanced diabetes) and a higher mortality rate than the general population. The economic burden of RA is substantial for patients and society since onset often occurs during the most productive years of life.

RA cannot be cured. Current treatments can only reduce disease activity or induce symptomatic remission. The main classes of drugs used in the treatment of RA are: non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional and biologic Disease modifying anti-rheumatic drugs (DMARDs).

The current treatment pathway is to start with conventional DMARDs (methotrexate for example) as first line therapy (alone or in combination), with NSAIDs to relieve symptoms. Patients failing to respond to at least two conventional DMARDs (one of which should be MTX), and have active disease, can progress to treatment with anti-TNFα agents.

Nearly 30% of patients have an insufficient response or intolerance to a first anti-TNFα agent. The current treatment options in the NHS for these patients are restricted to either rituximab or another anti-TNFα agent ("cycled anti-TNFα therapy"). Return to conventional DMARDs/supportive care is not considered a clinically relevant treatment pathway as these patients have advanced disease and have failed multiple conventional DMARDs.

The use of cycled anti-TNFα agents is common in England and Wales, even if supported by very limited efficacy data (and, to date, not by NICE). The practice of cycling currently used anti-TNFα agents (etanercept, infliximab, adalimumab) has not been studied in randomised controlled trials (RCTs). Furthermore, observational data suggest that the efficacy of a second anti-TNFα agent is considerably reduced, particularly in patients who have never responded to an anti-TNFα agent. This often contributes to treatment discontinuation, further switches and sub-optimal efficacy.

Though recommended by NICE, rituximab is also limited in its application: it has a restricted indication in patients with severe RA (as opposed to moderate to severe); and a significant number of patients will have an inadequate response to rituximab. In addition, the potential for long-lasting B-cell depletion with rituximab limits the use of alternative biologic treatments in non-responders. Rituximab also shows reduced efficacy in rheumatoid factor (RF) and/or anti-cyclic citrullinated protein (CCP) negative patients. Importantly, RF- patients represent 25% of the target population. Furthermore, the clinical evidence of long term efficacy or safety for rituximab is limited, particularly for repeated courses of treatment. Rituximab re-treatment regimen is ill-defined and is based on the recurrence of symptoms (flares), which further exposes patients to disease progression and use of health care resources. Lastly, rituximab mandates the co-administration of intravenous glucocorticoids to prevent the risk of acute and potentially fatal infusion reactions.

Given these data, efficacy and safety limitations, there is a large unmet need for alternative biologic options. This need is met by abatacept which exhibits a different mode of action from either rituximab or anti-TNFα agents. Abatacept is indicated in

patients with **moderate to severe** active RA and an insufficient response or intolerance to DMARDs, including at least one anti-TNFα agent. Abatacept consists of a soluble fusion protein that has been rationally designed for the treatment of autoimmune diseases such as RA. It is a fully humanised protein and works by modulating T-cell costimulation without inducing depletion of T cells or other leukocytes.

Abatacept Clinical Effectiveness

The clinical rationale and effectiveness of abatacept is clear and has been recognised within NICE's first appraisal. Abatacept should be recommended as first choice biologic agent in this patient population for the following reasons:

- Robust RCT evidence in the target population demonstrates its efficacy regardless of prior anti-TNFα usage or primary and secondary failure;

- Proven long-term efficacy and safety in the target population (up to 5 years) with sustained/improved clinically meaningful responses resulting in stable disease control over time;

- Within an extensive clinical programme (>4,100 RA patients) abatacept has proven efficacy in all stages of disease, consistently demonstrating a strong benefit:risk ratio. Radiographic evidence confirms that 50% of patients show no progression of structural damage up to 5 years;

- Significant improvements in all domains of quality of life, physical function and patient reported outcomes (reduced fatigue and pain, improved sleep quality and usual activity);

- Favourable safety profile based on data from 10,365 patient years showing abatacept to be generally safe and well tolerated.

- A wash out period is not required before switching from anti-TNFα therapy to abatacept. Unlike rituximab, abatacept does not limit subsequent treatment options;

- Abatacept has a fixed dose regimen per body weight range and is administered as a convenient, single and quick 30 minutes intravenous infusion every 4 weeks providing sustained disease control. Unlike rituximab, abatacept does not require pre-medication nor resuscitation facilities.

A total of six, placebo-controlled RCTs were deemed relevant to this submission, addressing a broad range of treatment scenarios. In the absence of head-to-head RCTs, a mixed treatment comparison (MTC) of the RCT evidence using placebo as the common comparator was undertaken to compare abatacept with rituximab, tocilizumab and golimumab. However, there were insufficient data to estimate reliably the relative treatment effect for a number of outcomes. The estimates that were derived from the MTC had very wide credibility intervals and a high level of uncertainty and should be interpreted with caution. Unadjusted cross-study comparisons of open label and long term data were also undertaken.

This submission will focus on a comparison of abatacept to rituximab and current anti-TNFα agents (etanercept, infliximab, adalimumab). In addition, a comparison will be made to the new biologic therapies (certolizumab pegol, tocilizumab, golimumab), although their price and place within the clinical setting is as yet unknown.

Comparisons of abatacept with rituximab

- Abatacept and rituximab have RCT evidence evaluating efficacy over 6 months. In addition, abatacept has extensive observational data evaluating its efficacy over 5 years (and 7 years in the methotrexate inadequate responders population). In contrast, rituximab efficacy evidence is limited to only 3 treatment courses with 24-week follow up, with no efficacy data on repeated treatment in patients who failed to respond to the initial course;

- Simple comparisons of abatacept and rituximab at one year demonstrate higher rates of response for abatacept than for rituximab;

- Abatacept has demonstrated similar efficacy regardless of RF status (MTX-IR) or prior anti-TNFα history (number, type or reason for failure). In contrast, rituximab has shown reduced efficacy in RF- and/or anti-CCP- compared to RF+ and/or anti-CCP+ patients.

At 6 months the probabilities of achieving LDAS, remission, the mean change from baseline in HAQ and the SF-36 physical component score (PCS) were numerically higher for abatacept than rituximab. The probabilities of withdrawal due to adverse events (AEs), withdrawals for any reason, and the number of serious infections were numerically higher for rituximab than for abatacept.

Simple comparisons of the long term extensions (LTEs) of ATTAIN and REFLEX at one year (based on post-hoc analysis) showed abatacept to have superior clinical benefit over a single course of rituximab for all efficacy outcomes, most importantly for the clinically relevant outcomes of LDAS and DAS28-defined remission. LDAS rates at one year for abatacept were 29% compared to 24% for rituximab. DAS remission rates at one year for abatacept were 16% compared to 12% for rituximab. One year ACR20 responses for abatacept were 75% whereas for rituximab data reported for both one and two courses were 45% and 54% respectively.

Comparisons of abatacept with cycled anti-TNFα agents

- There are no RCTs demonstrating the efficacy of current cycled anti-TNFα agents in the target population, whereas abatacept has robust RCT evidence demonstrating its efficacy regardless of prior anti-TNFα use;

- The limited observational data on cycled anti-TNFα agents suggest that patients are less likely to respond to a second anti-TNFα agent and significantly less to a third agent.

There is no RCT evidence evaluating the efficacy and safety of current cycled anti-TNFα agents (infliximab, adalimumab and etanercept) and certolizumab within the UK, therefore no formal comparisons with abatacept were possible. Thus data from the BSRBR on cycled anti-TNFα agents were considered most representative of the UK RA patient population. Simple unadjusted comparisons of cycled anti-TNFα agents from the BSRBR show mean HAQ changes from baseline to be greater for abatacept at one year. Limited RCT data were only available for golimumab (GO AFTER). A MTC of GO AFTER and ATTAIN trials showed that the probability of achieving an ACR50 and HAQ-DI response was numerically higher for abatacept than for golimumab (50.4% vs.. 34.0% and 20.3% vs.. 18.3% respectively). The place of golimumab within the clinical setting is as yet unknown. It is currently being reviewed by NICE in a separate Single Technology Appraisal (STA) which is anticipated in October 2009.

Comparisons of abatacept with tocilizumab

Evidence comes from two placebo-controlled randomised trials over a 6 month period, ATTAIN and RADIATE. The probabilities of withdrawal due to adverse

events and withdrawal for any reason were numerically higher for tocilizumab than for abatacept. The number of serious infections and any infections was numerically higher for tocilizumab than for abatacept. Tocilizumab is also associated with, gastrointestinal perforation, hepatotoxicity, hyperlipidaemia and haematological abnormalities. This requires regular monitoring with blood tests, dose adjustments or interruption of therapy (with risk of flare) and potentially concomitant lipid lowering medication with statins. The place of tocilizumab within the clinical setting is as yet unknown. It is currently being reviewed by NICE in a separate STA which is anticipated in October 2009.

Abatacept Cost Effectiveness

- Abatacept is backed by stronger and more extensive clinical evidence than its competitors, supporting a position as the biologic agent of first choice in patients with moderate to severe RA and an insufficient response or intolerance to one anti-TNFα agent. This clinical profile makes for a compelling value proposition for abatacept, and this is supported in this submission by health economic evidence that shows that abatacept is cost-effective as first biologic agent after one anti-TNFα agent vs. rituximab and cycled anti-TNFα agents.

Importantly, the conclusions of the cost-utility model presented as reference case for abatacept in the UK are consistent with those derived from different complementary modelling approaches also provided, and with those of health technology assessments conducted in Europe and around the world.

The cost-effectiveness of abatacept in anti-TNFα insufficient responders was compared with rituximab and current cycled anti-TNFα agents (etanercept, adalimumab and infliximab) using a patient-level simulation model. Comparisons with new biologic therapies (golimumab, certolizumab pegol and tocilizumab) were not possible because price information is not available.

The results of this cost-utility sequential model show that in RA patients with an insufficient response or intolerance to one anti-TNFα agent, abatacept is cost effective compared with both rituximab and with a basket of anti-TNFα agents, with cost per QALYs of £20,438 and £23,019, respectively. The results were tested in one-way sensitivity analyses and found to be robust to variations in most parameters. Probabilistic sensitivity analyses of the likelihood of the cost per QALY for abatacept compared with rituximab and cycled anti-TNFα agents below the £30,000 threshold are 99% and 97% respectively.

Regarding the budgetary impact, it is estimated that considering drug cost alone, positive NICE guidance for abatacept would result in a minimal net cost to the NHS in England and Wales estimated between £693,371 to £566,236 in 2010 depending on whether it displaces cycled anti-TNFα agents and rituximab or anti-TNFα agents alone. This impact appears to be minimal.

Conclusion

Abatacept, within its licensed indication, should be the first choice biologic agent for patients with an insufficient response or intolerance to one anti-TNFα agent:

- Only abatacept presents long-term efficacy and safety data up to 5 years in the target population. Abatacept has demonstrated sustained/improved clinical efficacy over time and favourable safety profile in this target

population. The monthly dosing treatment regimen with abatacept provides sustained and stable disease control in contrast to the rituximab flare-based regimen.

- Abatacept has a distinct mechanism of action that offers an important therapeutic option to manage insufficient response or intolerance to previous therapies, in a chronic disease which routinely requires the sequential use of different agents.

- Economic analyses also demonstrate that abatacept is cost-effective as a first biologic compared with both rituximab and cycled anti-TNFα agents for patients with insufficient response or intolerance to first anti-TNFα agent. Furthermore, it is estimated that the incremental cost to the NHS of NICE recommending abatacept would be minimal.

- Given the considerable clinical and economic burden of RA, providing access abatacept as first biologic of choice in patients with moderate to severe active RA and an insufficient response or intolerance to one anti-TNFα agent would address their specific condition and significant unmet needs, and allow this limited patient population to benefit from an effective, safe and cost effective therapeutic option.