COMMISSIONING SUPPORT

Appraisals

www.sph.nhs.uk/appraisals
Tel: +44 (0)1865 334787
Email: askappraisals@sph.nhs.uk

National Institute for Health and Clinical Excellence
Level 1A, City Tower
Piccadilly Plaza
Manchester M1 4BD

11th April 2011

Dear Mr Powell

Regarding: Abatacept for treatment of rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs

On behalf of the Commissioning Support, Appraisals Service (CSAS), I would like to submit our comments on the appraisal consultation document for the Single Technology Appraisal on Abatacept for treatment of rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs in the NHS in England and Wales. CSAS is in agreement with the appraisal committee's decision that this technology does not represent a cost effective use of scarce NHS resources.

- Unit costs: Abatacept is supplied in 250mg vials at a cost of £242.17 (excluding VAT; 'British National Formulary' BNF edition 61) and the prescribed dose is 500-1000mg (10mg/kg) administered on weeks 0, 2, 4, and thereafter every 4 weeks.
- Affordability: The CSAS rapid evidence review estimated that an average PCT of 300,000 could expect to have 2400 people with rheumatoid arthritis, 10% of whom would be eligible for biologicals, and 49% of whom approximately 118 patients - would be able to take and tolerate methotrexate alongside abatacept. The manufacturer has estimated that the annual drug cost for a person weighing between 60 and 100kg will be £10,171 in the first year and £9,445 in subsequent years. The estimated annual cost to treat 118 patients based on this revised costing is £1.2 million in the first year and £1.1 million annually thereafter. The Evidence Review Group (ERG) also estimates the cost per administration at £158.
- Efficacy: The ERG discussed the four RCTs identified in the manufacturer's submission and the mixed treatment comparison. In three RCTs (AIM, Kremer and IM101-119), abatacept plus methotrexate proved superior to placebo plus methotrexate in reducing disease activity; only AIM and Kremer were included in quantitative analyses. One three-arm RCT compared abatacept with placebo and with infliximab (all plus methotrexate; the ATTEST trial), and found abatacept to have better efficacy than infliximab. Both the AIM and the ATTEST studies found that abatacept plus methotrexate reduced disease activity at six months compared with placebo plus methotrexate (mean difference in DAS28 [28-joint disease activity score] vs. placebo: AIM, n=656: -1.15, 95% CI -1.38 to -0.91; ATTEST, n=431: -1.04, 95% CI -1.42 to -0.67). More patients treated with abatacept showed an improvement in disease activity, measured as DAS28 change ≥1.2 (RR vs. placebo: AIM: 1.62, 95% CI 1.39 to 1.88; ATTEST: 1.58, 95% CI 1.29 to 1.93). Several other DAS parameters and measures of

disease activity using American College of Rheumatology (ACR) response criteria ACR20/50 and 70 were improved with abatacept at six months and at one year follow-up. There was greater improvement in HAQ (Stanford Health Assessment Questionnaire) disability score at six months and one year with abatacept versus placebo and meta-analysis undertaken by the ERG estimated relative improvements in clinically meaningful HAQ response with abatacept versus placebo (six months: RR 1.46, 95% CI 1.27 to 1.67; one year: RR 1.65, 95% CI 1.41 to 1.94). The manufacturer's mixed treatment comparison of 11 trials comparing abatacept plus methotrexate with five biological DMARDs (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) plus methotrexate, demonstrated similar efficacy of abatacept to most other DMARDs, and better efficacy of abatacept compared with that in the trials included in meta-analysis. As the mixed treatment comparison also omitted key trials and included trials of participants with different baseline characteristics it was viewed with caution by the Appraisal Committee.

- Quality of the evidence: The quality of the three trials included in quantitative analysis was fully assessed by the manufacturer and by the evidence review group. The included studies have also been appraised by Cochrane reviewers in a recent review of abatacept for rheumatoid arthritis. Both the Kremer study and the AIM study were considered to be at high risk of bias because of methods of imputation and exclusion of non-adherent patients from analyses, respectively.
- Safety: There was no significant difference between abatacept (10mg/kg) and placebo in rates of serious adverse events at 6 or 12 months. Abatacept was associated with lower rates of serious adverse events, lower discontinuation rates and lower rates of both serious infections and acute infusional events than infliximab.
- Cost effectiveness: The Appraisal Committee considered a model submitted by the manufacturer, based on cost utility analyses over a lifetime horizon and from the healthcare provider prospective in which abatacept was compared with conventional DMARDs, all other biological DMARDs, and infliximab plus methotrexate. Abatacept and infliximab were dominated by adalimumab and certolizumab pegol in patients who could receive a subcutaneous injection. In patients who could not receive a subcutaneous injection, infliximab was extendedly dominated by abatacept and a conventional DMARD at a cost per QALY of £29,888 compared with conventional DMARDs alone. Although the ICER for abatacept is below the accepted threshold of cost effectiveness used for NHS therapies, some of the key assumptions were of concern to the ERG, and the Appraisal Committee felt that the concerns about the base case of the model were important and that plausible ICERs would in fact be greater than £30,000 per QALY. Specific concerns related to the methodological quality and presentation of the economic evaluation were:
    - The model was more complex than most seen previously by the ERG.
    - The use of HAQ scores instead of DAS-28, the mapping of HAQ scores to EQ-5D utility values, failure to include patient disutility in attending for infusions and assumptions around how disease progresses on and off different treatments.
    - Structurally the model did not allow the use of multiple biological DMARDs and did not therefore reflect current UK practice.
    - In the base case, the model did not allow dose escalation with abatacept although this had been included for infliximab and etanercept.
    - The model did not allow for vial sharing of infliximab.

Many of the assumptions made by the manufacturer in modeling favoured abatacept. ICERs from modeling with more 'realistic assumptions' (according to the ERG or in the manufacturer's sensitivity analyses) always increased to above £29,700 per QALY. In particular, sensitivity analyses demonstrated a large effect of the time horizon. The time horizon in the manufacturer's base case was the lifetime and sensitivity analyses demonstrated that changing this to five years had a large effect on the ICER, changing it from £29,900 per QALY gained in the manufacturer's base case to £84,400. Overall the ACD concluded that a model that combined plausible assumptions would produce ICERs that exceeded the range that represented an effective use of NHS resources.

- Additional factors:
    - The manufacturer indicated that denying intravenous treatment to people who require/request it on the grounds of age, disability or ethnic race would be unfair. The Committee considered that many of the patients who were identified in the submission as being unsuited to subcutaneous pharmacotherapy would be able to receive subcutaneous therapy administered by nursing personnel in the home. As a result, the ACD concluded that the manufacturer's definition of this group was not relevant for clinical practice in the UK and that this did not present an equality issue.
    - The ACD acknowledges the importance of choice for people who have inadequate response to initial DMARD treatment, and accept that the choice of a biological with a mechanism of action other than TNF inhibition may be important for people who cannot take these drugs.

If you require any further information please contact CSAS at; AskAppraisals@sph.nhs.uk

Yours sincerely

[redacted]

[redacted]
NHS Birmingham East and North
Email: [redacted]

[redacted], Solutions for Public Health
Tel: [redacted]
Email: [redacted]