Cost-effectiveness of subcutaneous abatacept (Orencia®), in combination with methotrexate (MTX), for the treatment of moderate to severe active rheumatoid arthritis in adult patients.

The NCPE has issued a recommendation regarding the use of SC abatacept in rheumatoid arthritis following inadequate response to conventional DMARD treatment. The NCPE does not recommend reimbursement of SC abatacept at the current price.

The HSE has asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the manufacturers (BMS) economic dossier on the cost-effectiveness of Orencia®, in combination with MTX, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate or a tumour necrosis factor-alpha (TNFα) inhibitor. The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examine all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **November 2013**

Bristol Myers Squibb submitted a dossier for SC abatacept (Orencia®) on 28th June 2013. Final clarifications were received on 1st October 2013. The company are seeking reimbursement under the high technology drugs scheme (HTDS).

1. The economic evaluation presented compared treatment with subcutaneous (SC) abatacept to treatment with other biologic treatments (intravenous abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) and conventional DMARDs. The population included adult patients who had responded inadequately to previous therapy with one or more DMARDs including MTX or a tumour necrosis factor-alpha (TNFα) inhibitor. The dossier presented the perspective of the Health Service Executive (HSE).

2. SC abatacept was compared to conventional DMARDs (methotrexate) and also to the biological treatments following failure of DMARDs and as second line treatment following failure of first line biological agent. The biological DMARDs included intraveneous abatacept, adalimumab, etanercept, infliximab, certolizumab pegol and golimumab. The treatment sequence included nine biological treatments which were randomly assigned following failure of first line biological (subcutaneous abatacept, intraveneous abatacept, adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and rituximab). Patients continue sequencing through each biological until all have been tried, at which point they move to a DMARD sequence (leflunomide, cyclosporin, azathioprine) and finally palliative care. A shorter biological sequence was explored in sensivity analysis.

3. Intravenous abatacept has been licensed for some time and therefore clinical trials demonstrating the benefit in rheumatoid arthritis have previously been published. Randomised controlled trials of subcutaneous abatacept have been presented demonstrating non-inferiority to the intravenous formulation. One head-to-head study versus subcutaneous adalimumab has also been presented. Comparative effectiveness evidence has been provided via a mixed treatment comparison with the other biological DMARDs considered for first line use. A mixed treatment comparison was performed to provide an estimate of relative efficacy (HAQ and DAS 28) and discontinuations due to adverse effects between the biological treatments. The review group had some concerns with the data used for the MTC; inclusion and exclusion criteria were not included in the dossier and reasons for exclusion of specific papers was not provided. The TEMPO trial was included for

etanercept which is confounded by the inclusion of methotrexate patients who had not experienced treatment failure, leading to a greater response in the placebo arm than would otherwise be expected. The review group reanalysed the MTC and these estimates of relative effectiveness were used in the model.

4. The cost effectiveness of SC abatacept was estimated using a cost utility model. The patient simulation model has a similiar structure to the BRAM model where benefit is applied through the HAQ index. Patients enter the model on a biologic treatment and if an adverse effect or lack of response occurs they switch to an alternative biological treatment. The review group consider the assumption that patients accrue the same benefit on starting on any line of treament as the second line, as potentially optimistic; this has been explored in sensitivity analysis.

5. Resource costs included drug, administration, dispensing and monitoring costs. A cost per unit HAQDI score is included to capture the cost of disability (€1,382). Utility values are included for an Irish cohort who were on biological therapy. Utility is applied through HAQ improvements using coefficients measured in an Irish cohort. The initial HAQ improvement is determined from clinical trial data (combined in the MTC) followed by a lesser long term HAQ improvement.

6. An ICER is presented for each biological therapy versus DMARDs. In the basecase presented by BMS the ICERs vs. DMARDs were **€69,670/QALY (incremental costs and QALYs €193,408 and 2.78 respectively for SC abatacept**, €68,350/QALY for golimumab, €75,029/QALY for etanercept, €85,161/QALY for infliximab, €75,565/QALY for adalimumab, €68,128/QALY for certolizumab and €94,337/QALYfor IV abatacept. As the review group had concerns over the manner in which the effectiveness of the treatments were calculated the review group requested that different inputs be used (MTC analysis performed by the review group where abatacept studies were included in the analysis reported in Schmitz *et al*.) BMS resubmitted the ICERs (biological vs. DMARD) using these inputs; **SC abatacept €79,510/QALY (incremental costs €197,873 and QALY 2.49)**, golimumab €71,476/QALY, etanercept €63,353/QALY, infliximab €95,138/QALY, adalimumab €82,830/QALY, certolizumab €73,315/QALY and IV abatacept. €109,655/QALY.

7. One way sensitivity analysis (OWSA), probabalistic analysis and scenario analysis were presented. OWSA was presented on a number of parameters for

abatacept versus DMARDs; those parameters with most impact were the HAQ coefficient and constant in the mapping equation, HAQ mortality ratio, pharmacist monthly dispensing care fee, cost of hospital outpatient appointment and cost per unit HAQ score. Most variation was in relation to the HAQ coefficients which varied the ICER from €64,595/QALY to €73,551/QALY. Scenario analysis was provided where the treatment sequence included less biologicals (two anti-TNF treatments followed by rituximab and tocilizumab). This analysis yield lower ICERs however the analysis was based on the BMS MTC effectiveness estimates which the review group had concerns about.

8. The probabilistic sensitivity analysis indicates that abatacept SC has a probability of cost effectiveness of approximately 40% at a willingness to pay threshold of €55,000/QALY. DMARDs have the highest probability of cost effectiveness below this threshold.

9. The estimated gross budget impact estimated by BMS (including cost of loading in the first year) is €1,146,175 in 2013, €3,360,090 in 2014, €5,522,528 in 2015, €7,500,720 in 2016 and €8,855,704 in 2017. The cumulative 5 year gross budget impact is €26,385, 217. The incremental (net) budget impact assuming switching from all other SC anti-TNFs is -€235,157 in 2013, -€440,994 in 2014, -€709,860 in 2015, -€830,850 in 2016 and -€1,019,825 in 2017. The cumulative 5 year net budget impact is estimated to be -€3,236,686. The net budget impact assumes that all patients will be switched from another biological therapy however the review group consider this to be an unlikley scenario and therefore the savings are likely to be overestimated.

10. The most plausible ICER calculated for abatacept SC vs. DMARD is likely to be €79,510/QALY. As this ICER is above the agreed threshold the NCPE do not consider this product to be cost effective at the current price.