NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Health Technology Appraisal

The use of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis

Scope

Objectives:

(1) To review and update as necessary guidance to the NHS in England and Wales on the clinical and cost effectiveness of etanercept and infliximab which was issued in March 2002. [1] In line with their licensed indications at that time, etanercept and infliximab were appraised as treatments of active rheumatoid arthritis (RA) in adults when the response to treatment with existing disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate.

The original guidance will remain in place unless and until any new guidance has been issued. The review will consider whether any new evidence that has become available justifies a change to the original guidance.

(2) As part of the review, to conduct an appraisal of the clinical and cost effectiveness of etanercept and infliximab in the treatment of severe, active and progressive RA in adults in line with their current licensed indications.

(3) Adalimumab has been referred to the Institute by the Department of Health and Welsh Assembly Government. Consequently as part of the review, we will conduct an appraisal of the clinical and cost effectiveness of adalimumab in the treatment of moderate to severe active RA in adults when the response to DMARDs has been inadequate. We will also conduct an appraisal of adalimumab for early RA in line with its anticipated licence extension.

Background:
RA is a chronic disabling condition characterised by inflammation of the synovial tissue of the joints, causing pain, swelling and stiffness and progressive joint destruction. It affects between 0.5% and 1% of the population, or approximately 400,000 people in England and Wales. Of these, approximately 15% have severe disease.

Treatment aims to control pain and inflammation, and reduce joint damage, disability and loss of function, thereby improving quality of life. It involves a combination of pharmacological and non-pharmacological interventions. Conventional drug therapy relies on various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and DMARDs. Evidence suggests that DMARDs should be used soon after diagnosis and methotrexate is often used as initial therapy. Non-drug therapies include surgery, physiotherapy, and occupational therapy.

The technologies:
Tumour necrosis factor alpha (TNFα) is a pro-inflammatory mediator. Its over-expression is one of the factors responsible for the damaging processes which affect

[1] National Institute for Clinical Excellence (2002) Guidance on the use of etanercept and infliximab for the treatment of rheumatoid arthritis. *NICE Technology Appraisal Guidance* No. 36. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk

articular cartilage and bone. Adalimumab, etanercept, and infliximab all inhibit the activity of TNFα.

Adalimumab (Humira, Abbott Laboratories Ltd) is licensed for the treatment of moderate to severe, active RA in adults when the response to DMARDs, including methotrexate, has been inadequate. The marketing authorisation for adalimumab stipulates that to ensure maximum efficacy, adalimumab should be given in combination with methotrexate. Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. It is administered by subcutaneous injection. It is anticipated that the licence will be extended within the timeframe of the appraisal to include the treatment of patients with early RA.

Etanercept (Enbrel, Wyeth Pharmaceuticals) is licensed for the treatment of active RA in adults when the response to DMARDs, including methotrexate (unless contraindicated), has been inadequate, and for the treatment of *severe, active* and *progressive* RA in adults not previously treated with methotrexate. It is administered by subcutaneous injection.

Infliximab (Remicade, Schering-Plough Ltd) is licensed for the reduction of signs and symptoms as well as the improvement in physical function in patients with active disease when the response to disease-modifying drugs, including methotrexate, has been inadequate. It is also licensed for the treatment of *severe*, *active* and *progressive* RA in adults not previously treated with methotrexate or other DMARDs. Infliximab is only licensed for use in combination with methotrexate. It is administered by intravenous infusion.

Interventions	Adalimumab, etanercept and infliximab.
Population	Adults (18 years or over) with rheumatoid arthritis.
Current standard comparators	Management strategies with or without TNFα inhibitors. Other TNFα inhibitors.

Other considerations	The interventions will be appraised according to their licensed indications, taking into account proposed licence extensions. It is the Institute's policy however, not to issue guidance documentation on pharmaceuticals that do not hold a marketing authorisation in the UK for the relevant indication. Outcomes to be considered include: • physical function • joint damage • pain • adverse effects of treatment • health-related quality of life If the evidence allows, the impact of differences in the mode of administration on both patient preference and service delivery will also be considered. Data from the Biologics Registry established by the British Society for Rheumatology will be considered to explore the longer-term efficacy of these agents as well as their potential for adverse events. If the evidence allows, the appraisal will attempt to identify criteria for selecting patients for whom these treatments would be particularly appropriate, and the stage in the pathway of care when these technologies should be used. If the evidence allows, the appraisal will attempt to examine the consecutive use of TNFα inhibitors. It is anticipated that individuals may also be treated with other therapies; where the evidence permits any resulting confounding factors will be taken into consideration. The time horizon for the economic evaluation should reflect the chronic nature of the condition.

Related NICE recommendations:	National Institute for Clinical Excellence (2002) Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis. Technology Appraisal No. 35. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk National Institute for Clinical Excellence (2002) Guidance on the use of infliximab for Crohn's disease. Technology Appraisal No. 40. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk National Institute for Clinical Excellence (2003) Anakinra for rheumatoid arthritis. NICE Technology Appraisal Guidance No. 72. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk National Institute for Clinical Excellence (2001). Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis. NICE Technology Appraisal Guidance No. 27. London: National Institute for Clinical Excellence. Available from: www.nice.org.uk. There is an ongoing review of this appraisal. Efalizumab and etanercept for the treatment of psoriasis. Technology Appraisal. Expected date of issue: October 2005 Etanercept and infliximab for the treatment of psoriatic arthritis. Expected date of issue: October 2005 Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis. Expected date of issue: December 2006

Current NICE guidance	1.1 Etanercept and infliximab (infliximab only in combination with methotrexate) are recommended as options for the treatment of adults who have continuing clinically active rheumatoid arthritis that has not responded adequately to at least two disease-modifying anti-rheumatic drugs, including methotrexate (unless contraindicated). 1.2 Both etanercept and infliximab should be prescribed in accordance with relevant sections of the British Society for Rheumatology (BSR) guidelines, April 2001 (see Appendix D), which set out criteria for eligibility, definitions of failure of standard therapy, exclusion criteria and criteria for withdrawal of therapy. In particular, treatment should be withdrawn in the event of severe drug-related toxicity or because of lack of response at 3 months. 1.3 Prescription of these agents and follow-up of treatment response and adverse events should be undertaken only by a consultant rheumatologist specialising in their use. The choice of which of the two agents is used should be determined by consultation between the patient and the clinician responsible, taking into account differences in treatment schedules and patient preferences. 1.4 Maintenance therapy with these agents in those who respond to treatment initially should be at the lowest licensed dose compatible with continuing clinical response. 1.5 All clinicians prescribing etanercept or infliximab should (with the patient's consent) register the patient with the Biologics Registry established by the BSR and forward information on dosage, outcome and toxicity on a 6-monthly basis. 1.6 There is currently no evidence to support treatment beyond 4 years. A decision to continue therapy should therefore be contingent on ongoing monitoring of disease activity and clinical effectiveness in individual cases. Outcomes from the BSR Biologics Registry will help inform such decisions. 1.7 There is no evidence for the consecutive use of these agents, and therefore this is not recommended.