1 Guidance

1.1 On the balance of its clinical benefits and cost effectiveness, anakinra is not recommended for the treatment of rheumatoid arthritis, except in the context of a controlled, long-term clinical study.

1.2 Patients currently receiving anakinra for RA may suffer loss of well being if their treatment were discontinued at a time they did not anticipate. Therefore, patients and their consultants should continue therapy with anakinra until they consider it is appropriate to stop.

2 Clinical need and practice

2.1 Rheumatoid arthritis (RA) is a chronic, progressive, destructive and disabling condition that is associated with considerable morbidity and mortality, impacts severely on quality of life, and represents a considerable economic burden. RA affects all aspects of life, from education and employment through to family and social lives. It is estimated that 40% of people with RA stop working within 5 years of diagnosis.

2.2 RA is characterised by inflammation of the synovial tissue in joints, which causes pain, swelling and stiffness and can lead to joint destruction. Approximately 15% of people with RA have a particularly severe form of the disease that manifests as relentless pain and swelling, causing severe disability and loss of function.

2.3 RA is the most common inflammatory polyarthritis in the UK, and affects between 0.5% and 1% of the population. Recent estimates indicate an annual
incidence of 0.2 per 1000 population and a prevalence of 8 per 1000 population. On the basis of these estimates, approximately 400,000 people in England and Wales have RA.

2.4 Management of RA is holistic and multidisciplinary, with physical therapy and surgical intervention running in parallel with drug treatment. Key aims of treatment include controlling joint pain and inflammation, reducing joint damage, disability and loss of function, and maintaining or improving quality of life.

2.5 Conventional drug therapy for RA relies on various combinations of non-steroidal anti-inflammatory drugs, analgesics, corticosteroids and disease-modifying anti-rheumatic drugs (DMARDs). Evidence suggests that patients with RA should be treated with DMARDs soon after diagnosis, because patients in whom DMARD treatment is delayed have worse outcomes. DMARDs act to ameliorate symptoms and slow progression of structural damage; they are conventionally used in sequence. There are several DMARDs in use, but current best practice is initial treatment with methotrexate. Increasingly, combinations of DMARDs are used, although evidence in favour of combining DMARDs is limited.

2.6 The tumour necrosis factor α (TNFα) inhibitors etanercept and infliximab are currently recommended for people with continuing, clinically active RA that has not responded adequately to at least two DMARDs, including methotrexate (unless contraindicated). This patient subgroup has the greatest level of unmet clinical need and incurs the greatest proportion of direct medical costs. It is this same group that may benefit from treatment with anakinra.

3 The technology

3.1 Interleukin-1 (IL-1) is a pro-inflammatory cytokine that has been identified as a key molecule in the pathogenesis of RA. Its over-expression is one of the
factors responsible for the damaging inflammatory processes that occur in RA and for promoting cartilage destruction and bone resorption.

3.2 Anakinra (Kineret; Amgen) is a recombinant, non-glycosylated form of human IL-1-receptor antagonist that inhibits the activity of IL-1, thus protecting both cartilage and bone. It is licensed for use in combination with methotrexate in patients who have had an inadequate response to methotrexate alone. Anakinra is administered by subcutaneous injection at a dose of 100 mg once daily.

3.3 Anakinra costs £20.47 per day (excluding VAT; *Monthly Index of Medical Specialities*, October 2002), equivalent to £7450 per annum.

4 Evidence and interpretation

The Appraisal Committee (Appendix A) considered evidence from a number of sources (see Appendix B).

4.1 Clinical effectiveness

4.1.1 Five randomised controlled trials (RCTs) of anakinra in patients with RA were identified, involving a total of 2905 patients (2146 of whom received anakinra). Two of these trials evaluated the use of anakinra as monotherapy, anakinra is only licensed for use in combination with methotrexate. Three of the trials evaluated the use of anakinra in combination with DMARDs. All five trials were of high quality. Of the trials of anakinra in combination with DMARDs, one was at the licensed dose of anakinra (Trial A), one was not at the licensed dose (Trial B) and another was primarily a safety study (Study C). The results of Trials A and B are discussed here.

4.1.2 In the key trial that matched the licensed indication for anakinra (Trial A), 906 patients were randomised to receive either methotrexate plus placebo or methotrexate plus anakinra, 100 mg/day, for 52 weeks. At 24 weeks there was a statistically significant difference in ACR20 response rate in favour of
anakinra (38% vs 22%, \( p \leq 0.001 \)). ACR50 response rates were 17% for anakinra and 8% for placebo (\( p = 0.001 \)), and ACR70 response rates were 6% and 2%, respectively (\( p = 0.024 \)). (ACR20/50/70 response rates relate to 20%, 50% and 70% improvement in American College of Rheumatology symptom scores, respectively – see Appendix C.)

4.1.3 At 24 weeks, there was a statistically significant difference in change in HAQ score (Health Assessment Questionnaire functional ability score, see Appendix C) in favour of anakinra (−0.29 vs −0.18, \( p < 0.05 \)). There was no difference in the rate of withdrawals (22% vs 27%, \( p > 0.05 \)). Injection-site reactions were the most common adverse event, occurring in 65% and 24% of patients receiving anakinra and placebo respectively. Although these reactions were generally mild-to-moderate and transient, they led to withdrawal in 8% and 1% of patients respectively. Infectious episodes occurred in 33% and 26% of patients, and serious adverse events were reported by 4% and 3% of patients respectively.

4.1.4 The primary endpoint at 52 weeks was joint damage as measured by radiographic progression. Treatment with anakinra resulted in a statistically and clinically significant reduction in change from baseline in total Modified Sharp score (see Appendix C) compared with placebo (1.70 units vs 2.64 units, \( p < 0.001 \)). This result suggests that anakinra may inhibit the progression of structural damage of both bone and cartilage.

4.1.5 Similar results were reported in Trial B, in which anakinra at doses of 1 and 2 mg/kg/day (equivalent to 70 and 140 mg/day for a 70-kg adult) plus methotrexate were compared with placebo plus methotrexate. ACR20 responses at 12 weeks were 46% and 38% for the groups treated with anakinra 1 and 2 mg/kg/day respectively, compared with 19% for controls (\( p = 0.001 \) and \( p = 0.007 \) respectively). At 24 weeks, differences in ACR20 responses were statistically significantly different only for the 1 mg/kg/day group compared with controls (42% vs 23%, \( p = 0.018 \)).
4.1.6 There are no head-to-head trials comparing anakinra with either etanercept or infliximab. The results of an indirect comparison, which need to be interpreted with caution, suggest that anakinra may be significantly less effective at relieving the clinical signs and symptoms of RA, as measured by ACR20, than the TNFα inhibitors (risk difference −0.21, 95% CI −0.32 to −0.10).

4.1.7 In summary, anakinra in combination with methotrexate appears to be more effective than methotrexate plus placebo in the treatment of RA, based on ACR20 response rates. Reductions in HAQ scores were relatively small, but potentially clinically significant. Recently available data on radiographically assessed joint damage suggest a protective effect of treatment on disease progression. Injection site reactions were extremely common with anakinra, but overall serious adverse events were similar for the groups treated with anakinra or placebo.

4.2 Cost effectiveness

4.2.1 No published economic evaluations were found. The Assessment Group developed its own economic model, the Birmingham Rheumatoid Arthritis Model (BRAM), which is a revised version of the model used in the appraisal of etanercept and infliximab. The manufacturer’s submission also included an economic analysis of anakinra.

4.2.2 The Assessment Group model assessed the cost effectiveness of adding anakinra to a treatment pathway for RA. The following assumptions were made. Patients follow a fixed sequence of DMARDs, with progression based on loss of effectiveness or intolerable adverse events. HAQ scores improve on starting a DMARD and this improvement is lost on stopping the DMARD. While on treatment, patients experience a constant decline in their condition independent of the treatment they are receiving. For each DMARD there is a fixed start-up cost, which takes account of monitoring costs, followed by a constant annual usage cost. Utilities are based on HAQ score. Patients are
followed through to death, with the risk of death based on current HAQ score, age and sex.

4.2.3 A number of different scenarios were modelled, based on:
- whether anakinra is used in the middle or at the end of the DMARD sequence
- two different DMARD sequences
- whether etanercept is available for use.

For the eight possible scenarios, incremental cost-effectiveness ratios (ICERs) for anakinra ranged from £67,400 to £604,000 per quality-adjusted life-year (QALY). A scenario based on British Society for Rheumatology guidelines, with anakinra used third in a sequence of DMARDs that excludes etanercept and infliximab, increased the ICER to between £495,000 and £952,000 per QALY depending on the DMARD sequence used.

4.2.4 A number of sensitivity analyses that favoured anakinra were explored, including separate effectiveness estimates for each TNFα, incorporating costs associated with hospitalisations and joint replacement, increasing the time spent on anakinra (from 1.8 to 5.8 years), omitting the one-off loss of QALYs at the start and end of DMARD treatment, and improving the effectiveness of anakinra (from 0.375 to 0.5 initial HAQ improvement). In univariate sensitivity analyses, the lowest ICER was £54,400 per QALY.

4.2.5 The base case analysis is subject to a number of uncertainties and conservative assumptions, in particular the time spent on each DMARD, and the effect of DMARDs on disease progression and quality of life. In addition, the model does not include non-drug-related healthcare costs. The base case analysis, therefore, may give a conservative estimate of the cost effectiveness of anakinra. However, extensive sensitivity analyses suggest that it is unlikely that any reasonable changes to the model would reduce the ICERs significantly.
4.2.6 A Markov model to assess the cost effectiveness of anakinra over a 5-year period for patients for whom conventional DMARDs were no longer effective was included in the manufacturer’s submission. Patients progress between six different health states based on HAQ score, with a further possibility of death. Costs are based on health state, and include the costs of DMARDs and the associated costs of monitoring, as well as wider health-service costs. Utility values are taken from a study using the EQ-5D questionnaire in a group of 192 patients in a rheumatology outpatient clinic.

4.2.7 The model submitted by the manufacturer gives a base-case ICER of £16,545 per QALY. This result is robust to a number of one-way sensitivity analyses. An updated version of the manufacturer’s model, based on newly available data from the key clinical trial of anakinra (Trial A) gives an ICER of between £20,510 and £21,752 per QALY.

4.2.8 There are a number of limitations within the model, and a number of assumptions that do not reflect the results of clinical trials. For example:

- in the original model, response and progression rates for anakinra-treated patients were taken from trials that did not use the licensed dose
- the revised model overestimates the ACR20 response rate compared with the 6-month response rate observed in the trial (trial A).
- progression rates for the comparator arm are the same as those for a group of non-responders who are assumed to receive no benefit from DMARDs.

Individual sensitivity analyses that address some of these limitations have the effect of increasing the ICER for anakinra.

4.3 **Consideration of the evidence**

4.3.1 The Committee reviewed the data available on the clinical and cost effectiveness of anakinra for RA, having considered evidence on the nature of the condition and the value placed on the benefits of anakinra from people
with RA, those who represent them, and clinical experts. It was also mindful of the need to take account of the effective use of NHS resources.

4.3.2 The results of the available clinical trials provide evidence of a clinically significant benefit associated with anakinra. The committee was aware that 6 month outcome data from a large pragmatic trial of anakinra in a clinical practice setting were available. This was not submitted by the manufacturer because they believed an analysis of this data from the point of view of clinical effectiveness would not be of value as the study was set up to evaluate safety issues only. The Committee considered that despite these concerns the data from this study would have been useful in their deliberations. Irrespective of the potential importance of the pragmatic study the Committee – noted that there are very limited data to support the efficacy of anakinra beyond 1 year.

4.3.3 The Committee also accepted on balance that indirect comparisons of anakinra with etanercept and infliximab, although needing to be interpreted with caution, suggest that anakinra may be less effective at relieving the clinical signs and symptoms of RA than the TNFα inhibitors.

4.3.4 The Committee discussed whether there might be a useful role for anakinra in treating those people for whom TNFα inhibitors are unsuitable or in whom such treatment has failed to produce an adequate response. However, there is currently no substantial evidence to support the use of anakinra in the treatment of this subgroup.

4.3.5 The Assessment Group’s economic model provides an upper estimate of the cost effectiveness of anakinra. The Committee noted the degree of uncertainty in key variables, such as the effect of DMARDs on disease progression and the omission of non-drug-related healthcare costs from the model.

4.3.6 Using the efficacy estimates for each of the DMARDs and biologics which the committee felt to be the most reliable, the assessment report model showed
that the cost per QALY of adding anakinra to the portfolio of therapies for RA was in excess of £69,000.

4.3.7 The model submitted by the manufacturer provides a lower estimate of the cost effectiveness of anakinra. However, the Committee noted that the optimistic assumptions in the manufacturer’s model undermined the robustness of the results. In particular, the Committee questioned the appropriateness of the comparator group, and the response and progression rates for patients treated with anakinra.

4.3.8 The Committee concluded that, although there was evidence of the clinical effectiveness of anakinra in the short term, the extent of the benefit was not sufficient to justify its cost. On this basis, the Committee was not able to recommend anakinra for routine use in adults with RA.

5 Recommendations for further research

5.1 Further studies are required to evaluate the long-term efficacy and safety of anakinra. Such studies should evaluate the impact of anakinra on disease progression, health-service utilisation and mortality. Comparative trials of anakinra with other DMARDS and TNF\(\alpha\) inhibitors are required to identify comparative efficacy and guide clinical practice. In particular, the role of anakinra in the treatment of people for whom TNF\(\alpha\) inhibitors are unsuitable, or in whom such treatment has failed to produce an adequate response, needs to be established.

5.2 Further research is also needed to improve the reliability and understanding of radiographic outcomes in clinical trials. In particular, the relationship between the effectiveness of newer therapies on radiographic outcomes and their effects on clinical outcomes needs to be explored further.
5.3 Longitudinal data on the quality of life of people with RA, and the impact of anakinra and other interventions on quality of life are required to improve the reliability of economic analyses.

6 Preliminary views on the resource impact for the NHS

6.1 This guidance is not expected to result in a net increase in NHS expenditure or to impact on other resources. The budget impact will depend on the number of, and funding arrangements for, controlled clinical studies in which anakinra is used.

7 Implementation and audit

This section presents proposals for implementation based on the preliminary recommendation in Section 1.

7.1 Clinicians treating people with active RA should review their current practice in line with the guidance in Section 1. Anakinra should be used for the treatment of RA only in the context of controlled, long-term clinical studies.

7.2 Local clinical guidelines, protocols or care pathways for the care of people with RA should incorporate the guidance.

8 Related guidance

8.1 The Institute has issued guidance on the use of COX II-selective inhibitors for osteoarthritis and rheumatoid arthritis, and etanercept and infliximab for rheumatoid arthritis:


9 Proposed date for review of guidance

9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.

9.2 The guidance on this technology is reviewed in June 2006.

Professor David Barnett
Chair, Appraisal Committee
June 2003
Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month other than in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declaration of interests, are posted on the NICE website.

Dr Jane Adam
Radiologist, St George’s Hospital, London

Dr Sunil Angris
General Practitioner, Waterhouses Medical Practice, Staffordshire

Dr Darren Ashcroft
Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester
Professor John Brazier
Health Economist, University of Sheffield

Professor John Cairns
Professor of Health Economics, Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen

Professor Mike Campbell
Statistician, Institute of General Practice & Primary Care, Sheffield

Dr Peter I Clark
Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Wirral, Merseyside

Dr Mike Davies
Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Dr Cam Donaldson
PPP Foundation Professor of Health Economics, School of Population and Health Sciences & Business School, Business School – Economics, University of Newcastle upon Tyne

Professor Jack Dowie
Health Economist, London School of Hygiene and Tropical Medicine

Dr Paul Ewings
Statistician, Taunton & Somerset NHS Trust, Taunton

Ms Sally Gooch
Director of Nursing, Mid-Essex Hospital Services NHS Trust, Chelmsford

Professor Trisha Greenhalgh
Professor of Primary Health Care, University College London
Dr George Levyy
Lay Representative; Chief Executive, Motor Neurone Disease Association, Northampton

Dr Gill Morgan
Chief Executive, NHS Confederation, London

Professor Philip Routledge
Professor of Clinical Pharmacology, College of Medicine, University of Wales, Cardiff

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Mr Miles Scott
Chief Executive, Harrogate Health Care NHS Trust

Professor Andrew Stevens (Vice-Chair)
Professor of Public Health, University of Birmingham

Professor Mary Watkins
Professor of Nursing, University of Plymouth

Dr Norman Waugh
Senior Lecturer and Public Health Consultant, University of Southampton
B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Tina Eberstein
Technical Lead, NICE project team

Christopher McCabe
Technical Lead, NICE project team

Nina Pinwill
Appraisals Project Manager, National Institute for Clinical Excellence
Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration, University of Birmingham.


B The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope and assessment report. They are also invited to comment on the ACD and consultee organisations are provided with the opportunity to appeal against the FAD.

I Manufacturer/sponsors:

- Amgen Limited

II Professional/specialist and patient/carer groups:

- Arthritis Care
- Arthritis & Musculoskeletal Alliance
- Arthritis Research Campaign
- British Health Professionals in Rheumatology
- British Institute of Musculoskeletal Medicine
- British Society for Rheumatology
- Chartered Society of Physiotherapy
- College of Occupational Therapists
- Department of Health
- National Rheumatoid Arthritis Society
- Primary Care Rheumatology Society
- Royal Association for Disability & Rehabilitation
- Royal College of General Practitioners
Royal College of Nursing
Royal College of Physicians
Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- British National Formulary
- NHS Quality Improvement Scotland
- Northampton Primary Care Trust

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee’s deliberations. They gave their expert personal view on anakinra for RA by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD.

- Mrs Ailsa Bosworth, Chair, National Rheumatoid Arthritis Society.
- Dr Robin Butler, Chair, Arthritis & Musculoskeletal Alliance; Consultant Rheumatologist, Robert Jones and Agnes Hunt Orthopaedic Hospital.
- Mr Hywel Evans, Policy and Campaigns Manager for Wales, Arthritis Care.
- Professor David Scott, Consultant Rheumatologist, Norfolk and Norwich University Hospital.
- Ms Dawn Stobbs, Chair, National Association of Rheumatology Occupational Therapists.
Appendix C. Measures of clinical effectiveness

**American College of Rheumatology response criteria**

The American College of Rheumatology (ACR) definition of response requires an improvement in both the tender joint count and swollen joint count, and an improvement in at least three of:

- global disease activity assessed by observer
- global disease activity assessed by patient
- patient assessment of pain
- physical disability score, for example the HAQ (see below)
- acute phase response, for example erythrocyte sedimentation rate or C-reactive protein.

Response is defined as ACR20/50/70, where the numbers refer to the percentage improvement required in clinical measures.

**Health Assessment Questionnaire**

HAQ is a measure of functional ability and is measured on a scale of 0 (best) to 3 (worst). It is a self-administered measure that evaluates four dimensions: disability, discomfort, drug side effects and costs. In addition to assessing activities of daily living, the HAQ quantifies the degree of assistance required by patients.

**Modified Sharp score**

The Modified Sharp score is a measure of joint damage as assessed radiographically, and is based on joint space narrowing and erosions.