NHS

National Institute for Clinical Excellence

National Institute for Clinical Excellence

11 Strand
London
WC2N 5HR

Web: www.nice.org.uk

N0016 50k 1P July 01 (ABA)

Technology Appraisal Guidance - No.27

NHS

National Institute for Clinical Excellence

Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis

July 2001

Technology Appraisal No. 27

Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis

Issue date: July 2001
Review date: May 2004

Ordering Information
Copies of this Guidance can be obtained from the NHS Response Line by telephoning 0870 1555 455 and quoting ref. N0016. A patient version of this document can be obtained by quoting ref. N0018. A bi-lingual patient leaflet is also available ref. N0019.

Distribution of Guidelines

This document has been circulated to the following:

- Health Authority Chief Executives in England and Wales
- NHS Trust Chief Executives in England and Wales
- PCG Chief Executives
- Local Health Group General Managers
- Medical and Nursing Directors in England and Wales
- GPs in England and Wales
- Consultant Geriatricians in England and Wales
- Rheumatologists in England and Wales
- Chief Pharmacists, Heads of Drug Purchasing, Heads of Drug Information, Pharmaceutical Advisors, GP Prescribing Advisors and Purchase Advisors in England and Wales
- NHS Director Wales
- Chief Executive of the NHS in England
- NHS Executive Regional Directors
- Special Health Authority Chief Executives
- Community Health Councils in England and Wales
- Patient Advocacy Groups
- Commission for Health Improvement
- NHS Clinical Governance Support Team
- Chief Medical, Nursing Officers and Pharmaceutical Officers in England and Wales
- Medical Director & Head of NHS Quality – National Assembly for Wales
- Representative bodies for health services, professional organisations and statutory bodies, Royal Colleges

---

This Guidance is written in the following context:
This guidance represents the view of the Institute which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

National Institute for Clinical Excellence

11 Strand
London
WC2N 5HR

Web: www.nice.org.uk

ISBN: 1-84257-114-1
Published by the National Institute for Clinical Excellence
July 2001

Technology Appraisal
Guidance No. 27

Issue Date July 2001
Review Date May 2004

National Institute for Clinical Excellence

Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis

This section (Section 1) constitutes the Institute's Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis. The remainder of the document is structured in the following way:

The full document and a Summary of Evidence are available from our website at www.nice.org.uk or by telephoning 0870 1555 455 and quoting the reference number N0016.

Mae'r adran hon (adran 1) hefyd ar gael yn Gymraeg ar ein gwefan neu drwy gysylltu â 0870 1555 455, rhif cyfeirnod N0017.

1. Guidance

1.1 Cox II selective inhibitors and other non-steroidal anti-inflammatory drugs (NSAIDs) are indicated for pain and stiffness in inflammatory rheumatoid arthritis and for the short-term management of pain in osteoarthritis. All NSAIDs are associated with adverse events and should only be prescribed when there is a demonstrable clinical need and in accordance with their summary of product characteristics. Long-term use should be avoided without appropriate monitoring and re-evaluation of the clinical need.

1.2 Of particular concern is the propensity of NSAIDs, including the Cox II selective agents, to cause gastro-intestinal adverse events, which can include life threatening gastro-intestinal perforations, ulcers or bleeds. These agents should therefore only be prescribed after careful consideration of their risks and benefits, especially in patients who may be at increased risk of such adverse events.

1.3 Cox II selective inhibitors are not recommended for routine use in patients with rheumatoid arthritis (RA) or osteoarthritis (OA). They should be used, in preference to standard NSAIDs, when clearly indicated as part of the management of RA or OA only in patients who may be at 'high risk' of developing serious gastrointestinal adverse effects.

1.4 Patients at 'high risk' of developing serious gastrointestinal adverse events include those of 65 years of age and over, those using concomitant medications known to increase the likelihood of upper gastrointestinal adverse events, those with serious co-morbidity or those requiring the prolonged use of maximum recommended doses of standard NSAIDs (See Section 2.10). The risk of NSAID-induced complications is particularly increased in patients with a previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation. The use of even a Cox II selective agent should therefore be considered especially carefully in this situation.

1.5 In all patients with cardiovascular disease, there remains uncertainty over the use of Cox II selective inhibitors and they should not therefore be prescribed routinely in preference to standard NSAIDs where these are indicated in this group of patients. Furthermore, many patients with cardiovascular disease receive low dose aspirin and this carries an increased risk of gastro-intestinal events. In patients who are taking low dose aspirin, the benefit of using Cox II selective agents (to decrease gastrointestinal toxicity) is reduced. Prescribing Cox II selective agents preferentially over standard NSAIDs in this situation is therefore not justified on current evidence.

1.6 There is no evidence to justify the simultaneous prescription of gastro-protective agents with Cox II selective inhibitors as a means of further reducing potential gastrointestinal adverse events.

2 Clinical Need and Practice

2.1 Arthritis is a general term to describe the inflammatory or degenerative disease of one or more joints. Symptoms can include some or all of the following: pain, swelling, stiffness, restriction of movement and redness of the skin overlying the affected joint. RA and OA are the two most common forms. There are an estimated 1,325,000 –1,750,000 OA patients and 250,000-500,000 RA patients in England and Wales.

2.2 RA is a progressive, destructive condition, for which therapy aims to control inflammation, pain and associated symptoms, thereby increasing quality of life. In the management of RA, NSAIDs are often used for extended periods of time and frequently combined with disease modifying agents. OA is a chronic condition in which the principal pathology is degenerative change. Although some modification of disease progression is possible the main therapeutic end point is pain control with simple analgesics. NSAIDs are often used in the short term to control acute inflammatory episodes. They are probably of little benefit in long-term continuous use for OA, which is likely to lead to increased risk of potentially harmful adverse effects. In both OA and RA pain control facilitates compliance with other treatment modalities such as weight loss and physiotherapy, which may influence disease progression.

2.3 Non-drug treatment is considered an important component of management in OA and RA and it includes patient education, physical and occupational therapy, dietary advice, self-management programmes and weight loss.

2.4 Arthritis is a major cause of morbidity and disability in England and Wales and imposes a considerable financial burden on both patients and the NHS. The annual NHS expenditure on medical care for arthritis patients is estimated to be around £560m – £920m, excluding indirect costs.

2.5 In 1999, over 18.5 million NSAID treatments were prescribed in England and Wales for various indications, at a cost of approximately £170m. This does not include the costs of co-prescribing of gastroprotective agents. NSAIDs are also often used for conditions outside of their licensed indications and for pain not associated with inflammation.

2.6 All NSAIDs are believed to exert their anti-inflammatory and analgesic action by interfering with the formation of prostaglandins from their precursor (arachidonic acid) via inhibition of the catalysing enzyme cyclo-oxygenase (Cox). Prostaglandins are responsible for mediation of inflammation and pain, but also play a critical role in the protection of gastric mucosa, the support of renal function and in haemostasis through platelet activation.

2.7 NSAIDs are associated with upper gastrointestinal side effects, ranging from mild dyspepsia to more severe complications such as gastric haemorrhage and perforation, which lead to hospitalisation, surgery or even death. Therefore, these drugs potentially have an important impact on both patient quality of life and health care expenditure. According to some estimates, around 2,000 deaths due to NSAID related side effects during treatment for arthritis occur each year in the UK.

2.8 Peptic ulcers can be detected endoscopically in 10-20% of people taking standard doses of traditional NSAIDs and simple erosions of the gastric mucosa in a further 20-40%. It is not clear how these endoscopic findings relate to the reported gastrointestinal adverse effects of NSAIDs or to the more serious complications such as perforation, ulcer or bleeding (PUB).

2.9 Gastro-protective agents (GPAs) are often co-prescribed with NSAIDs, with the aim of reducing the associated gastrointestinal adverse effects. It is estimated that co-prescribing rates range from 17% to 34%. The most commonly used GPAs include proton pump inhibitors, H_2 receptor antagonists and misoprostol, a prostaglandin E1 analogue. However, these agents have been shown to be only partially effective in the prophylaxis and treatment of NSAID related gastrointestinal events. They are also not without additional side effects and add significantly to the total cost of drug therapy.

2.10 The following factors have been shown to be associated with a high risk of development of gastrointestinal complications following NSAID therapy:

- Age of 65 years and over;
- Previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation;
- Concomitant use of medications that are known to increase the likelihood of upper gastrointestinal adverse events e.g. steroids and anti-coagulants;
- Presence of serious co-morbidity, such as cardio-vascular disease, renal or hepatic impairment, diabetes and hypertension;
- Requirement for the prolonged use of maximum recommended doses of standard NSAIDs.

3 The Technology

3.1 There are at least two isoforms of cyclo-oxygenase: Cox I (constitutive enzyme) and Cox II (inducible enzyme). High concentrations of Cox I are found in platelets, vascular endothelial cells, the stomach and in kidney collecting tubules. It is responsible for the production of prostaglandins, which are essential for maintenance of normal endocrine function, renal function, gastric mucosal integrity and haemostasis. In contrast, under physiological conditions, Cox II is virtually undetectable in most tissues, but its activity may be significantly increased by inflammatory and mitogenic stimuli.

3.2 Cox II selective inhibitors 'selectively' block the Cox II iso-form of the cyclo-oxygenase enzyme, whilst largely sparing the Cox I iso-form. Inhibition of Cox I is thought to be principally responsible for the gastrointestinal adverse effects of NSAIDs.

3.3 There is wide variation in the reported Cox II selectivity of the NSAIDs, as assessed by different assay techniques, and therefore classification of these agents according to their selectivity remains problematic. Celecoxib and rofecoxib, two recently introduced Cox II inhibitors, are often classified as "Cox II specific agents" due to claims of higher Cox II selectivity compared to the more established NSAIDs, meloxicam and etodolac, which are often referred to as "Cox II selective". This guidance refers to all four drugs as 'Cox II selective inhibitors'.

3.4 Celecoxib and etodolac are licensed for symptomatic relief in the treatment of both OA and RA, whereas rofecoxib is licensed for OA only. Meloxicam is licensed for short-term symptomatic treatment of acute exacerbations of OA and long-term symptomatic treatment of RA.

3.5 The ranges of daily acquisition costs, based on the British National Formulary (September 2000) listed prices, are currently £0.33-£0.46 for meloxicam, £0.52 for etodolac, £0.61-£1.22 for celecoxib and £0.77 for rofecoxib. Consideration of differential daily acquisition costs should include the different dosage requirements for each drug within their licensed indications.

4 Evidence

Clinical Effectiveness

4.1 A total of 53 randomised controlled trials (RCTs) involving 61,731 patients with RA and OA were reviewed (14 rofecoxib, 15 celecoxib, 3 rofecoxib versus celecoxib, 9 meloxicam and 12 etodolac). These trials included both placebo and NSAID comparators (naproxen, diclofenac, ibuprofen, piroxicam, tenoxicam, nabumetone, nimesulide and aspirin).

4.2 There is evidence that the Cox II selective inhibitors referred to in this Guidance (rofecoxib, celecoxib, meloxicam and etodolac) are more effective than placebo and of equivalent efficacy to other NSAIDs in their ability to reduce pain (resting and active) and to improve physical and global function in both OA and RA patients.

4.3 There is evidence to suggest that, although the four Cox II selective inhibitors increase the incidence of gastrointestinal adverse events compared to placebo in both OA and RA patients, the magnitude of this effect is less than that of standard NSAID therapy.

4.4 Rofecoxib and celecoxib have been shown to be associated with a reduced incidence of gastric erosions on endoscopy compared to standard NSAIDs in patients with arthritis. However, the importance of this finding as a surrogate for the development of peptic ulceration or other major gastrointestinal adverse effects in patients treated with these drugs in routine clinical practice is uncertain.

4.5 Indirect comparison of the effects of meloxicam, rofecoxib and celecoxib relative to other NSAIDs based on available RCT evidence, does not demonstrate a difference in either efficacy or adverse events between them.

4.6 The RCT evidence for the incidence of gastrointestinal adverse events associated with etodolac compared to other NSAIDs cannot be considered conclusive as many of the studies were insufficiently powered to detect differences in serious gastrointestinal adverse events. There is however post-marketing data for etodolac, collected over 15 years, that provides pragmatic evidence of a reduced incidence of serious gastrointestinal events compared to standard NSAIDs. All of the Cox II selective agents exhibit some degree of dose dependency of the incidence of upper gastrointestinal adverse effects but published evidence indicates that the therapeutic window is much wider for rofecoxib and celecoxib than for meloxicam and etodolac.

4.7 Concerns have been raised over the cardiovascular and renal effects of Cox II selective inhibitors. In particular, this has been highlighted in the recent VIGOR trial (n=8,076), comparing rofecoxib and naproxen, which reported an increase in the number of myocardial infarctions in the rofecoxib group (0.4% compared to 0.1%; relative risk, 4.0: 95% CI, 1.1 to 14.2). However 38% of these infarctions occurred in only 4% of the trial patients who would have been candidates for cardio-prophylaxis with low-dose aspirin, but which was not permitted by the strict inclusion criteria for the study. There were however other patients on rofecoxib who suffered increased numbers of myocardial infarctions in the trial who were not, in retrospect, candidates for low does aspirin. The issue remains unresolved

and further research is required. This potential increased risk should, however, be taken into consideration when prescribing selective Cox II inhibitors in patients with cardiovascular disease, as is the case with all NSAIDs.

4.8 Aspirin in low dose is frequently indicated for the secondary prevention of thrombotic cerebrovascular or cardiovascular disease in the same patients who may also be at increased risk of the gastrointestinal complications which are associated with all NSAIDS, including aspirin. Co-prescription of aspirin with standard NSAIDs is known to increase the risk of such complications and evidence from the CLASS trial (n=8,059) suggests that the risk reduction of upper gastrointestinal events associated with Cox II selective inhibitors may not be evident when they are combined with aspirin. In this study, the annualised incidence rates of upper gastrointestinal complications alone and combined with symptomatic ulcers for celecoxib versus ibuprofen/diclofenac in 1,645 patients who were also taking low dose aspirin were 2.0% vs. 2.1% (p=0.92) and 4.7% vs. 6.0% (p=0.49). In the 6,323 patients, who were not receiving aspirin the rates for upper gastrointestinal complications were significantly lower for celecoxib (0.4% vs. 1.3 p=0.04), although in both aspirin and non-aspirin groups combined there was no significant difference in the annualised incidence of upper gastrointestinal complications (0.8% vs. 1.45% p=0.09). In the VIGOR study (n=8,076), in which concomitant aspirin was not permitted, the rates of confirmed upper gastrointestinal events (ulcers, perforations or bleeds) were found to be 2.1 and 4.5 per 100 patient years (relative risk, 0.5: 95% confidence interval 0.3 to 0.6, p<0.001) in the patients receiving rofecoxib or naproxen respectively.

4.9 No evidence was found to justify the simultaneous prescription of gastro-protective agents with Cox II selective inhibitors as a means of further reducing potential gastrointestinal adverse events. Furthermore, the relative benefits of combinations of standard NSAIDs with GPAs compared to Cox II inhibitors alone has not been determined.

4.10 In summary, in the absence of evidence of significant differences in anti-inflammatory efficacy between the Cox IIs and standard NSAIDs, the avoidance of serious adverse effects, particularly on the gastro-intestinal tract, becomes the most relevant factor when considering their use. For the most part the evidence suggests that the Cox II selective agents are less likely to produce symptomatic gastrointestinal tract adverse events. However, there remains some concern regarding the potential cardiovascular risks associated with the Cox II selective agents and therefore caution is needed, as it is for standard NSAID therapy, when prescribing in patients with pre-existing cardiovascular disease.

Cost effectiveness

4.11 There are three published cost-effectiveness studies on the selective Cox II inhibitors. Two of these compared meloxicam to modified release diclofenac, one in the UK and the other in a cross-national context (UK, Italy and France). The third compared the costs associated with the use of rofecoxib, celecoxib, ibuprofen, naproxen and diclofenac, in a simple decision analytic model based on local U.S. prices.

4.12 Economic evaluations submitted by the manufacturers generally report favourable incremental cost per gastrointestinal event averted and cost per life year gained (LYG) for the Cox II selective inhibitors versus standard NSAIDs in all (high and average risk) OA and RA patients. In the industry submissions, the upper limit of the cost per serious gastrointestinal event saved (i.e. perforation, ulceration and bleeding - PUB) ranges from £3,500 to £10,759 and LYG values for all patients range between £6,842 and £15,647.These models assume significant reductions in co-prescribing rates of GPAs with Cox II selective inhibitors and all but one model ignored non-gastrointestinal side effects. Two submissions assessed the use of Cox II selective agents in 'high-risk' patients and reported improved cost-effectiveness ratios when compared with conventional NSAIDs for this patient group.

4.13 A recent, but as yet unpublished, study commissioned by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), estimated higher, hence less favourable, cost effectiveness ratios than those submitted by the manufacturers in average-risk patients. In this study, celecoxib was dominated by diclofenac (i.e. celecoxib was more costly and less effective). In addition the estimated cost per LYG ratios for rofecoxib were greater than £150,000 when compared with standard NSAIDs in average-risk patients. The CCOHTA report also includes incremental cost per quality adjusted life year (QALY) estimates for celecoxib and rofecoxib versus standard NSAIDs. These cost per QALY estimates were again not favourable for average-risk OA and RA patients, but became so for the 'high risk' group. These results support the potential for enhanced cost effectiveness of these agents in the 'high risk' group of patients. There are no other cost per QALY estimates available to date.

4.14 In summary, there is insufficient evidence in the literature to conclude specifically on the differential clinical effectiveness of the various Cox II selective inhibitors or of their differential risk of causing adverse upper gastrointestinal events in ‘high risk’ patients. Evidence from economic models and the fact that the absolute number of gastrointestinal events averted is likely to be greater for ‘high risk’ than for other patients indicates that the cost-effectiveness of the Cox II selective inhibitors would be more favourable in this ‘high risk’ group.

5 Implications for the NHS

5.1 The total budget impact of this guidance in the NHS in England and Wales will depend on a number of factors, including the extent of the reduction in GPA prescription, the relative risk reduction of gastrointestinal adverse events in high risk patients on changing to Cox II selective inhibitors, and the rate of uptake of the Cox II selective inhibitors.

5.2 Switching high-risk OA and RA patients to Cox II selective inhibitors would lead to an annual incremental cost of approximately £25 million to the NHS. This figure is based on the following assumptions: half of the 'high risk' patients will be offered Cox II selective inhibitors; each product has an equal market share of 25%; the proportion of patients aged over 65 is 58% for OA and 45% for RA; the percentage of patients with previous gastrointestinal events is 8%; the average treatment duration is 180 days a year; and the relative risk reduction is constant across different risk groups.

6 Related Guidance

6.1 The Institute issued guidance on the use of Proton Pump Inhibitors in the treatment of dyspepsia in June 2000. The Institute's clinical guideline for treatment of dyspepsia is in development.

7 Further Research

7.1 There is a paucity of good quality comparative 'head to head' randomised clinical trials of Cox II selective inhibitors in the treatment of arthritis, especially in patients at high risk of developing serious gastrointestinal adverse events. The sub-groups of patients who are likely to benefit most from Cox II inhibitors need to be clearly defined.

7.2 There is a need for methodologically robust cost-effectiveness studies, possibly using data from 'head to head' trials. These trials should specifically focus on adverse events and incorporate quality of life outcomes.

7.3 The effectiveness of Cox II selective inhibitors in arthritis patients on low-dose aspirin treatment should also be further investigated.

8 Implementation

8.1 Primary Care Groups, Local Health Groups and Trusts should take account of the acquisition costs of the individual products in determining the local prescribing practice of these selective Cox II inhibitors.

8.2 The use of Cox II selective inhibitors, and all other NSAIDs, outside of licensed indications should be discouraged. A significant proportion of the severe gastrointestinal events caused by NSAID treatment could be avoided by targeting appropriate patients.

8.3 To enable clinicians to audit their implementation of this guidance, it is recommended that treatment outcomes be recorded for each patient receiving Cox II selective inhibitors who subsequently experience gastrointestinal adverse events and that these events are reported to the CSM through the 'yellow card scheme'.

8.4 This information should be incorporated into local clinical audit data recording systems, and consideration given (if not already in place) to the establishment of appropriate categories in routine electronic record keeping systems used in primary care groups and hospitals.

8.5 Prospective clinical audit programmes should record the extent to which the recommendations of this guidance are implemented. Such programmes are likely to be more effective in improving patient care when they form part of the organisation's formal clinical governance arrangements and where they are linked to specific educational and training activities.

9 Review of Guidance

9.1 This guidance will be reviewed in May 2004.

Andrew Dillon
Chief Executive

July 2001

APPENDIX A

Appraisal Committee Members

The Appraisal Committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend one or the other. Declared interests may also exclude a member from individual technology appraisals. The committee are supplemented by technology specific experts as indicated in Appendix B.

Professor R. L. Akehurst
Dean, School of Health Related Research
Sheffield University

Professor David Barnett (Chairman)
Professor of Clinical Pharmacology
University of Leicester

Professor Sir Colin Berry
Professor of Morbid Anatomy
St Bartholomew's and Royal London School of Medicine

Dr Sheila Bird
MRC Biostatistics Unit,
Cambridge

Professor Martin Buxton
Director of Health Economics Research Group
Brunel University

Professor Yvonne Carter
Professor of General Practice and Primary Care
St Bartholomew's and Royal London School of Medicine

Dr Karl Claxton
Lecturer in Economics
University of York

Professor Duncan Colin-Jones
Professor of Gastroenterology
University of Southampton

Professor Sarah Cowley
Professor of Community Practice Development
Kings College, London

Dr Nicky Cullum
Reader in Health Studies
University of York

Mr Chris Evennett
Chief Executive
Mid-Hampshire Primary Care Group

Professor Terry Feest
Clinical Director and Consultant Nephrologist
Richard Bright Renal Unit and
Chairman of the UK Renal Registry

Ms Jean Gaffin
Formerly Executive Director
National Council for Hospice and Specialist Palliative Care Service

Mrs Sue Gallagher
Chief Executive
Merton, Sutton and Wandsworth Health Authority

Dr Trevor Gibbs
International Medical Operations Director
GlaxoWellcome R&D Ltd

Mr John Goulston
Director of Finance
The Royal Free Hampstead NHS Trust

Professor Philip Home
Professor of Diabetes Medicine
University of Newcastle

Dr Terry John
General Practitioner
The Firs, London

Dr Diane Ketley
Clinical Governance Programme Leader
Leicester Royal Infirmary

Dr Mayur Lakhani
General Practitioner, Highgate Surgery, Leicester and Lecturer,
University of Leicester

Mr M Mughal
Consultant Surgeon
Chorley and South Ribble NHS Trust

Mr James Partridge
Chief Executive
Changing Faces

Professor Philip Routledge
Professor of Clinical Pharmacology
University of Wales

Professor Andrew Stevens
Professor of Public Health
University of Birmingham

APPENDIX B

Sources of Evidence

The following documentation and opinion was made available to the Appraisals Committee:

a. Assessment report prepared by the NICE Appraisals Team

- The Clinical Effectiveness and Cost-Effectiveness of Celecoxib, Rofecoxib, Meloxicam and Etodolac (Cox-II Inhibitors) for rheumatoid arthritis and osteoarthritis, October 2000
- Assessment Report Addendum prepared by the NICE Appraisals Team, February 2001

b. Manufacturer/Sponsor submissions from:

- Boehringer Ingelheim
- Merck Sharp and Dohme
- Pharmacia and Pfizer
- Shire

c. Professional/Specialist Group and Patient Group submissions from:

- British Geriatrics Society
- Chartered Society of Physiotherapy
- Royal College of General Practitioners
- BLAR (Arthritis Care, Arthritis Research Campaign, British League Against Rheumatism, British Society for Rheumatology and Primary Care Rheumatology Society)

d. External expert and patient advocate submissions from:

- Professor David L Scott, Professor of Clinical Rheumatology, King's College, London
- Dr John Dickson, Business Manager, Primary Care Rheumatology Society
- Neil Betteridge, Head of Policy and Campaigning, Arthritis Care

APPENDIX C

Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis – Patient information

The patient information in this appendix has been designed to support the production of your own information leaflets. You can download it from our website at www.nice.org.uk where it is available in English and Welsh. If you would like printed copies of the leaflets please ring the NHS Response Line on 0870 1555 455 and quote reference number N0018 for the English patient leaflet and N0019 for the bi-lingual leaflet.

What is NICE Guidance?

The National Institute for Clinical Excellence (NICE) is a part of the NHS. It produces guidance for both the NHS and patients on the use of medicines, medical equipment, diagnostic tests and clinical and surgical procedures.

When the Institute evaluates these things, it is called an appraisal. Each appraisal takes around 12 months to complete and involves the manufacturers of the drug or device, the professional organisations and the national groups who represent patients and their carers.

NICE looked at the available evidence on the cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac and has provided guidance that will help the NHS in England and Wales decide when they should be used in the treatment of osteoarthritis and rheumatoid arthritis.

What is arthritis?

Arthritis is a general term used to describe a disease of the joints. Symptoms can include some or all of the following: pain, swelling, stiffness, difficulty in movement and redness of the skin over the affected joint. The two most common forms of arthritis are rheumatoid arthritis and osteoarthritis. There are 1,325,000 –1,750,000 people with osteoarthritis and 250,000-500,000 people with rheumatoid arthritis in England and Wales.

Rheumatoid arthritis is a condition in which the joints are inflamed and damaged over a long period of time. Treatment aims to improve quality of life by controlling the symptoms of the disease which can include inflammation (swelling of the joint) and pain. Non-steroidal anti-inflammatory drugs (NSAIDs) are often used, and they can be combined with other medicines that can alter the way the disease progresses.

Osteoarthritis is a form of arthritis that gradually damages the cartilage that lines the joints. Although some medicines are used with the aim of slowing down the disease, the main aim of treatment is to control pain with simple pain relieving drugs.

What are Cox II inhibitors?

Cox II inhibitors are a type of non-steroidal anti-inflammatory drug (NSAID) used for the short-term treatment of acute inflammation in the joints caused by arthritis. They include celecoxib (Celebrex) and etodolac (Lodine SR) which can be used for rheumatoid arthritis and osteoarthritis, rofecoxib (Vioxx) which is only used for osteoarthritis and meloxicam (Mobic) which is used for acute osteoarthritis and the long-term treatment of rheumatoid arthritis.

Cox II selective inhibitors and other non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat pain and stiffness in inflammatory rheumatoid arthritis and for the short-term management of pain in osteoarthritis.

What has NICE recommended?

Cox II selective inhibitors are not recommended for routine (regular) use in patients with rheumatoid arthritis or osteoarthritis.

They should only be used, instead of standard NSAIDs, in people with rheumatoid arthritis or osteoarthritis who may be at 'high risk' of developing serious gastrointestinal problems.

All NSAIDs can cause side effects (other problems) and they should only be prescribed when there is a demonstrable clinical need and they should only be used for the type of disease that they are licensed for. Long-term use of these products should be avoided unless the person taking the medicine is monitored and their condition is checked to see if these medicines are still required.

All NSAIDs, including the Cox II selective agents, can cause side effects such as gastro-intestinal problems (problems in the stomach or intestine). These problems can include stomach ulcers or bleeding, and possibly life threatening perforations (rips or holes) in the wall of the stomach or intestine. These drugs should therefore only be prescribed after a careful consideration of the risks and benefits for the person who would be taking them. Special care should be taken in people who are considered at a 'high-risk' of such gastro-intestinal problems.

People at 'high risk' of developing serious gastro-intestinal problems include:

- those aged 65 years and over;
- those using other medicines that are known to increase the likelihood of gastro-intestinal problems;
- those with some other diseases related to their osteoarthritis or rheumatoid arthritis (these are called serious co-morbidities); and
- those requiring the long term use of standard NSAIDs at the maximum dose.

What should I do?

If you, or someone you care for, has rheumatoid or osteoarthritis then you should discuss this advice at your next appointment.

Will NICE review its guidance?

Yes. The guidance will be reviewed in May 2004.

Further Information

Further information on NICE, and the full guidance on Cox II selective inhibitors, issued to the NHS is available on the NICE web site (www.nice.org.uk). The guidance can also be requested from 0870 1555 455, quoting reference N0016.

If you would like the full guidance on PPIs please quote reference 21492, and reference 21943 for the patient leaflet.

If you have access to the Internet and would like to find out more about osteoarthritis or rheumatoid arthritis please visit the NHS Direct website: www.nhsdirect.nhs.uk. If you would like to speak to NHS direct please call them on 0845 46 47.