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Cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs - etodolac, meloxicam, celecoxib, rofecoxib, valdecoxib and etoricoxib - for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation

NOTE: PRE PEER REVIEW VERSION

Produced by West Midlands Health Technology Assessment Collaboration

Authors Dr Yen-Fu Chen, Systematic Reviewer, Department of Public Health & Epidemiology, University of Birmingham

Dr Paresh Jobanputra, Consultant Rheumatologist, Department of Rheumatology, University Hospital Birmingham NHS Trust, Selly Oak Hospital

Dr Pelham Barton, Lecturer in Mathematical Modelling Health Economics Facility, Health Services Management Centre, University of Birmingham

Professor Stirling Bryan, Health Economics Facility, Health Services Management Centre, University of Birmingham

Ms Anne Fry-Smith, Information Specialist, Department of Public Health & Epidemiology, University of Birmingham

Dr Gwyn Harris, General Practitioner, Laurie Pike Health Centre, Birmingham

Dr Rod Taylor, Reader in Public Health and Epidemiology, Department of Public Health & Epidemiology, University of Birmingham

Correspondence to Dr Rod Taylor
West Midlands Health Technology Assessment Collaboration
Department of Public Health and Epidemiology
University of Birmingham
Edgbaston Birmingham

Tel: 0121 4142704
Fax: 0121 4147878
Email: r.s.taylor @bham.ac.uk

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About 'home unit'

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively undertake research synthesis to produce health technology assessments. Most of our members are based in the Department of Public Health & Epidemiology, University of Birmingham, however other members are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility, University of Birmingham, and pharmacists and methodologists from the Department of Medicines Management, Keele University.

WMHTAC produce systematic reviews, health technology assessments and economic evaluations for NHS R&D HTA programme (NCCHTA), the National Institute for Clinical Excellence (NICE), and for the health service in the West Midlands. WMHTAC also undertakes methodological research on research synthesis, and provides training in systematic reviews and health technology assessment.

Contributions of authors

Dr Yen-Fu Chen coordinated the clinical evidence aspects of the review, applied the inclusion and exclusion criteria, extracted data, appraised studies, conducted meta-analysis, wrote the body of the report and edited the report.

Ms Anne Fry-Smith carried out the searches.

Dr Paresh Jobanputra wrote the introduction and background, carried out data extraction, assisted in the identification of non-trial data inputs to the model and edited the report.

Dr Pelham Barton adapted the 'front end' to the Maetzel model, ran the assessment group model, wrote the model section and edited the report.

Professor Stirling Bryan appraised the industry models, wrote the review of economic studies and edited the report.

Dr Rod Taylor supervised the project, applied the inclusion and exclusion criteria, extracted data, appraised studies and conducted meta-analysis and drafted the discussion section of the report.

Conflicts of interest

Dr Paresh Jobanputra has received funding from Pfizer for two research studies: (1) Quality of care in patients with musculoskeletal pain who use NSAIDs; (2) Perception of risk in relation to NSAID use for patients with RA and OA. He has also been entertained, paid to speak and provided with financial assistance for educational purposes by many manufacturers of NSAIDs, new and old. Dr Rod Taylor has undertaken paid presentations for Pfizer, Canada and Novartis, UK not related to RA or OA management.

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Please note:

A number of sponsors submitted information to the National Institute for Clinical Excellence in confidence and references to this information have been removed from the report. However, it should be noted that the Institute's Appraisal Committee has access to the full report when drawing up their guidance.

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Epidemiology & background: Osteoarthritis and rheumatoid are common conditions that cause pain, disability and reduced physical function. Treatment costs of arthritis to the NHS are substantial, and rising. NSAIDs are effective treatments for symptomatic relief of arthritis. COX-2 selective NSAIDs have the potential for maintaining symptomatic benefits but also may reduce the adverse gastrointestinal effects associated with non-selective NSAIDs.

Number and quality of studies, and direction of evidence:
Celecoxib - 35 randomised controlled trials (RCTs) were included. Studies compared celecoxib to either placebo or non-selective NSAIDs. Compared to non-selective NSAIDs (naproxen or diclofenac), celecoxib (200 to 800mg/day) was equally efficacious and of superior GI tolerability. Celecoxib is associated with significantly fewer clinical GI events (RR: 0.64, 95% CI: 0.46 to 0.89) and complicated GI events (RR: 0.57, 95% CI: 0.34 to 0.97) and a significantly higher risk of myocardial infarction (RR: 1.87, 95% CI: 1.06 to 3.30).

Etodolac - 29 RCTs were included. Studies compared etodolac to either placebo or non-selective NSAIDs. Compared to non-selective NSAIDs (naproxen, piroxicam, diclofenac, indomethacin, tenoxicam, ibuprofen, nabumetone and or nimesulide), etodolac (600 to 1000 mg/day) was equally efficacious and of equivalent or superior GI tolerability. Pooled analysis did not show a difference in complicated GI clinical events (RR: 0.39, 95% CI: 0.13 to 1.24) or risk of myocardial infarction (RR: 0.50, 95% CI: 0.09 to 2.66) Etodolac was associated with significantly fewer clinical GI events (RR: 0.32, 95% CI: 0.15 to 0.71).

Etoricoxib – 7 RCTs were included. Studies compared etoricoxib to either placebo or non-selective NSAIDs. Compared to non-selective NSAIDs (naproxen, diclofenac and ibuprofen), etroricoxib (60 to 120mg/day) was equally efficacious and of equivalent or superior GI tolerability. Pooled analysis did not show a difference in clinical GI events (RR: 0.23, 95% CI: 0.5 to 1.08), complicated GI events (RR: 0.46, 95% CI: 0.07 to 3.10) or risk of myocardial infarction (RR: 1.58, 95% CI: 0.06 to 38.66).

Meloxicam - 16 RCTs were included. Studies compared meloxiocam to either placebo or non-selective NSAIDs. Compared to non-selective NSAIDs (naproxen, diclofenac, nabumetone or piroxicam), meloxicam (7.5 to 22.5 mg/day) was of inferior or equivalent efficacy and superior GI tolerability. Pooled analysis did not show a difference in clinical GI events (RR: 0.57, 95% CI: 0.38 to 1.08) or complicated GI events (RR: 0.52, 95% CI: 0.26 to 1.05). There was no trial evidence on myocardial infarction risk.

Rofecoxib- 25 RCTs were included. Studies compared rofecoxib to either placebo or non-selective NSAIDs. Compared to non-selective NSAIDs (naproxen, ibuprofen, arthrotec, combined diclofenac and misoprostol, or nabumetone), rofecoxib (12.5 to 50mg/day) was equally efficacious and had superior GI tolerability. Rofecoxib was associated with significantly fewer clinical GI events (RR: 0.43, 95% CI: 0.32 to 0.57) and complicated GI events (RR: 0.40, 95% CI: 0.23 to 0.74) and a significantly higher risk of myocardial infarction (RR: 2.92, 95% CI: 1.29 to 6.60).

Valdecoxib – 11 RCTs were included. Studies compared valdecoxib to either placebo or non-selective NSAIDs. In comparison to non-selective NSAIDs (naproxen or diclofenac), valdecoxib (10 to 80mg/day) was equally efficacious and had superior GI tolerability. Valdecoxib is associated with significantly fewer clinical GI events (RR: 0.12, 95% CI: 0.03 to 0.59) and complicated GI events (RR: 0.38, 95% CI: 0.17 to 0.86) and a significantly lower risk of myocardial infarction (RR: 0.23, 95% CI: 0.06 to 0.90).

There is a need for caution in the interpretation of the above meta-analysis results as relatively small numbers of clinical GI and MI events were reported across trials.

Subgroup analyses – Celecoxib reduces clinical GI events and significantly increases MI risk, relative to non-selective NSAIDs, in both aspirin users and non-users. Rofecoxib reduces clinical GI events, relative to non-selective NSAIDs, in both patients with prior GI history and no prior GI history, steroid users and non-users, and patients positive and negative for *H. pylor*. These subgroup analyses are based on small numbers and need confirmation. It is not possible to comment on the effect of use of anticoagulants and age on clinical GI or MI risk of COX-2 selective NSAIDs

Direct COX-2 comparisons – 7 RCTs were included. Studies compared rofexocib (12.5-25mg/day) to either celecoxib (200mg/day) or valdecoxib (10mg/day). Compared drugs were equally tolerable and of equal efficacy. There was no trial evidence comparing clinical GI events, complicated GI events and MI risk.

COX-2 versus non-selective NSAID combined with a gastroprotective agent– 1 RCT was identified that directly compared celecoxib to diclofenac combined with omeprazole. Arthritis patients who had recently suffered a GI haemorrhage were included. Although no significant difference in clinical GI events was reported, the number of events was small and more such studies, where patients genuinely need NSAIDs are required to confirm this data.

Cost & cost effectiveness:
Review of previous economic analyses - A review of previous published cost effectiveness analyses, principally comparing either celecoxib or rofecoxib to non-selective NSAIDs, indicated a wide of range of possible incremental costs per quality-adjusted life year gained (QALY).

The Assessment Group Model - The Assessment Group has undertaken a new modelling exercise that used the Markov model developed originally by Maetzel et al (2001) as a starting point. The model has been designed to run in two different forms: the 'full AGM', which includes an initial drug switching cycle, and the 'simpler AGM', where there is no initial cycle and no opportunity for the patient to switch NSAID.

Data Sources - The main data sources for clinical parameters are the meta-analysis results from our systematic review. Where necessary, we have used other sources.

Results - The base case incremental costs per QALY results for the simpler model are as follows:

COX-2 NSAID	Population and Comparator		
	Patients: standard[1] Comparator: NSAID[3] only	**Patients: standard[1] Comparator: NSAID[3] + PPI**	**Patients: high risk[2] Comparator: NSAID[3] + PPI**
Celecoxib (OA)	£132,000	Dominated[4]	Dominated[4]
Celecoxib (RA)	£673,000	Dominated[4]	Dominated[4]
Etodolac	£43,600	Dominated[4]	Dominated[4]
Etoricoxib	£29,800	£212,000	Dominated[4]
Meloxicam (OA)	£17,100	*£9,980*[5]	*£6,930*[5]
Meloxicam (RA)	£27,700	Dominated[4]	Dominated[4]
Rofecoxib	£97,500	Dominated[4]	Dominated[4]
Valdecoxib	£30,500	£3,500,000	Dominated[4]

1: age 58, no specific high risk factors; 2: prior GI ulcer; 3: diclofenac; 4: comparator costs lower and effects higher than COX-2 selective NSAID; 5: comparator effects and costs higher than COX-2 selective NSAID

Using the simpler AGM, with ibuprofen or diclofenac alone as the comparator, all of the COX-2 products are associated with higher costs (i.e. positive incremental costs) and small increases in effectiveness (i.e. positive incremental effectiveness), measured in terms of QALYs. The magnitude of the incremental costs and the incremental effects, and therefore the ICERs, vary considerably across all COX-2 seletive NSAIDs.

When the simpler AGM was run using ibuprofen or diclofenac combined with PPI as the comparator, the results change substantially, with the COX-2 selective NSAIDs looking generally unattractive from a cost-effectiveness point of view. This applies both to 'standard' arthritis patients and to 'high-risk' arthritis patients defined in terms of previous GI events.

The full AGM produced results broadly in line with the simpler model.

Limitations of the calculations: There are substantive differences in the incremental costs per QALY results in this report compared with industry submissions. These differences reflect, principally, variations in parameter values for clinical GI events and MI risk. There are also key differences in the choice of comparator non-selective NSAIDs and costs, and whether cardiovascular risks are included within the model.

Need for further research: With reduced costs of PPIs future primary research needs to compare effectiveness and cost effectiveness of COX-2 selective NSAIDs relative to non-selective NSAID with a PPI. Direct comparisons of different COX-2 selective NSAIDs, using equivalent doses, that compare GI and MI risk are needed. Pragmatic studies that include a wider range of people including the older age groups with a greater burden of arthritis and those at cardiovascular and renal risk are also necessary to inform clinical practice.

Conclusions: Compared to non-selective NSAIDs, COX-2 selective NSAIDs are more expensive and are associated with a wide range of costs per quality-adjusted life year gained (QALY) in patients with osteoarthritis and rheumatoid arthritis. Costs per QALY differ for each agent and whether the drug was to be used in someone at average or at high risk. Costs per QALY are also influenced by the choice of NSAID comparator and whether that NSAID is used in combination with a PPI.

Abbreviations & Definitions of Terms

COX-2 selective NSAIDs
For the purposes of this review the following NSAIDs are included in this category: celecoxib, etodolac, etoricoxib, meloxicam, rofecoxib, and valdecoxib. Diclofenac appears to have similar levels of COX-2 selectivity as some of these agents but is not included in this category.

ADVANTAGE	Assessment of Difference Between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness trial
BNF	British National Formulary
CI	Confidence interval
CLASS	Celecoxib Long-term Arthritis Safety Study
COX	Cyclooxygenase
Coxib	Refers to certain chemical classes of NSAID but does not necessarily mean COX-2 selectivity
CV	Cardiovascular
DMARD(s)	Disease modifying anti-rheumatic drugs
Dose regimens	od: once daily; bd: twice daily; tds: three times daily; qds: four times daily
EMEA	European Medicines Agency
FDA	United States Food and Drug Administration
H2RA	Histamine-2 receptor antagonist such as cimetidine or ranitidine
GI	Gastrointestinal
GORD	Gastro-oesophageal reflux disease
MELISSA	Meloxicam Large-Scale International Study Safety Assessment
mg	Milligram
MI	Myocardial infarction
MUCOSA	Misoprostol Ulcer Complications Outcome Safety Assessment
NICE	National Institute for Clinical Excellence
NNT	Number needed to treat
NNH	Number needed to harm
NSAID(s)	Non-steroidal anti-inflammatory drugs (excluding aspirin)
OA	Osteoarthritis
OR	Odds ratio
PPI	Proton Pump Inhibitors (such as omeprazole or lansoprazole)
PUB	Refers to symptomatic ulcers (see below) and complicated upper GI events (see below) combined
POB	Refers only to complicated upper GI events (see below)
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RR	Relative risk
SELECT	Safety and Efficacy Large-scale Evaluation of COX-inhibiting Therapies
SUCCESS	Successive Celecoxib Efficacy and Safety Studies
ug	microgram
UGI	Upper GI
VACT	Vioxx, Acetaminophen, Celecoxib Trial
VAS	Visual analogue scale
VIGOR	Vioxx Gastrointestinal Outcomes Research study

WOMAC	Western Ontario and McMaster Universities scale for assessment of knee or hip osteoarthritis

Symptomatic upper GI ulcers
Symptomatic upper GI ulcers defined as ulcers seen on endoscopy or radiographs with associated symptoms, for example where patients have been investigated for upper GI symptoms of dyspepsia during a study (i.e. evaluated 'for cause').

Complicated upper GI events
This includes perforations, obstructions and bleeding of the stomach and/or duodenum.

Serious cardiovascular thrombotic events
The definition by Antiplatelet Trialists' Collaboration is adopted. These include cardiovascular, hemorrhagic, and unknown death, nonfatal myocardial infarction, and nonfatal stroke.

1 AIMS OF THE REVIEW

1. To undertake a systematic review of the clinical effectiveness and cost-effectiveness of celecoxib, etodolac, etoricoxib, meloxicam, rofecoxib, and valdecoxib for osteoarthritis and rheumatoid arthritis.
2. To assess the cost-effectiveness of celecoxib, etodolac, etoricoxib, meloxicam, rofecoxib, and valdecoxib from a National Health Services (NHS) perspective.
3. To explore the potential impact of concomitant gastroprotective agents, with either COX-2 selectiveNSAIDs, or other non-selective NSAIDs, on the incidence of symptomatic gastrointestinal ulcers and complications such as bleeding, perforation, or gastric outlet obstruction.
4. To explore the impact of low dose aspirin (less than or equal to 325 mg per day) used in conjunction with COX-2 selective NSAIDs on the incidence of cardiovascular adverse events and symptomatic upper gastrointestinal ulcers and their complications.

AN ADDENDUM TO THIS REPORT FOR LUMIRACOXIB WILL BE PREPARED FOR 31st AUGUST 2004

2 BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective analgesics used commonly for musculoskeletal disorders such as osteoarthritis (OA), rheumatoid arthritis (RA), soft-tissue disorders, spinal pain, headaches (including migraine), menstrual disorders, and post-operative pain. Sales of ibuprofen, available over the counter and the most widely used NSAID, have increased as sales of aspirin and paracetamol have fallen.[1] The volume of prescribed NSAIDs has also increased and costs of prescription NSAIDs have increased by a quarter due to the use of cyclooxygenase-2 (COX-2) selective NSAIDs. Upper gastrointestinal (UGI) toxicity, especially gastric ulcers with complications such as haemorrhage and perforation, is an important public health problem that may be reduced by wider use of COX-2 selective NSAIDs. Current NICE guidance[2] recommends that COX-2 selective inhibitors:

- Should *not* be used
    a. routinely in patients with OA and RA
    b. in preference to non-selective NSAIDs in those with cardiovascular disease or those taking low-dose aspirin
    c. in combination with gastro-protective agents as a means of further reducing potential gastrointestinal (GI) adverse events
- Should be used in preference to non-selective agents in high risk patients such as
    a. those of 65 years or above
    b. those with serious co-morbidity
    c. those taking other medications known to increase the likelihood of upper GI adverse events
    d. those needing prolonged therapy with NSAIDs at maximal doses
    e. those with a history of previous gastric or duodenal ulcers, upper gut bleeding or perforation

About 6% of those over 65 years of age receive NSAIDs for at least three-quarters of a given year and up to 40% of this population at least one prescription for an NSAID.[3] The annual cost of prescribed NSAIDs is around £200 million per annum in England.[4]

2.1 Description of Health Problem

2.1.1 Osteoarthritis

Osteoarthritis (OA) is the commonest cause of musculoskeletal disability and joint replacement surgery. It may be defined as *a condition of synovial joints characterised by cartilage loss and evidence of an accompanying periarticular bone response*.[5] Definitions such as this - which need radiographic confirmation - ignore the clinical experience of OA and have limited clinical utility; especially in primary care where most patients are treated. Radiographic changes of OA at sites such as the spine are universal with ageing - age is the strongest determinant of radiographic, and clinical, OA. However the dissonance of symptoms and radiographic change, and the difficulties of defining OA, make it hard to estimate prevalence with confidence. For instance 15% of women between the ages of 55 and 64 have knee pain and 7% have radiographic knee OA (but not necessarily any pain).[6]

OA causes joint pain - often aggravated by physical activity; joint stiffness or gelling - often after periods of inactivity; and, joint swelling, deformity or enlargement. Patients might also experience creaking or crepitus in affected joints. Symptoms may arise as a result of joint injury, endocrine or metabolic disturbances, and developmental or heritable factors. The spine, certain finger and thumb joints, acromio-clavicular, hip, and knee joints are commonly affected by OA. Physical impairments due to OA vary greatly and depend, to a limited extent, on radiographic change: individual factors such as occupation, psychological adjustment, and degree of social support all have a bearing.[7]

The goals of treating OA are to relieve symptoms and improve functional limitations. At present no treatment seems to have a convincing, and clinically relevant, benefit in terms of delaying structural progression of established OA or to prevent development of OA in new joints.[8,9] Education about OA and advice on behaviour change, such as diets for weight reduction, may be successful for some and could even reduce the rate of deterioration. Others may need medication including analgesics and NSAIDs,[10] topical rubefacients, nutritional supplements and, occasionally, joint injections.[11] Physical therapy for muscle strengthening, walking aids and advice on appropriate exercises has an important role in clinical practice. For more advanced disease, especially involving the knee and hip, surgery including joint replacement, may be needed.

2.1.2 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic inflammatory disorder of unknown cause that mainly affects synovial joints. It has an annual incidence of 31 per 100,000 women and 13 per 100,000 men and a prevalence of 1.2% in women and 0.4% in men.[12] Disease incidence peaks in the sixth decade and RA is more common in women than men by a ratio of 2.5 to 1.

RA is diagnosed from a constellation of clinical, laboratory and radiographic abnormalities. The disease can cause pain, swelling and stiffness in a variety of joints including hands, wrists, the neck and large joints. Symptoms may begin within days or evolve over many weeks and are often worse in the morning. Other organ systems, such as the lungs, the pericardium, blood vessels and eyes may be also be affected with a potential for severe disability, systemic ill-health and life-threatening complications, in some cases. The severity of disease is variable; for instance in a community cohort 18% of patients were in remission, and on no treatment, after 3 years of follow-up. By contrast, nearly half had moderate disability at 3 years[13] and a quarter had a joint replaced after around 20 years.[14]

The goals of treating RA are also to relieve symptoms and improve functional limitations. Additional goals, attainable for RA with drug therapy, include reduction of structural joint damage.[15] Drugs used for RA include NSAIDs, analgesics, corticosteroids, and disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate; in varying combinations. Orthopaedic surgery, including joint replacement and soft tissue procedures, may be necessary and many professionals allied to medicine contribute to the care of patients with RA.[16]

2.1.3 Outcome measures for rheumatoid arthritis and osteoarthritis

Assessing outcomes in RA and OA is best done by relying on patient reports,[8,17] although some outcome scales have key elements that encompass physician judgements about disease status. In both OA and RA radiographic assessment of joint damage is also an important research tool: radiographic outcomes are better validated and accepted as relevant endpoints in RA.

At least two self completed questionnaires are used widely to assess pain, function and stiffness of knee and hip OA: the Lequesne and the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index; both combine responses in these three symptoms to yield a single measure. Many studies of OA also report pain alone or *patient global assessments,* using either a Likert scale or a 10 cm visual analogue scale (VAS). Global assessments may refer to overall disease status or response to a particular therapy. The latter allows patients and physicians to make an overall judgement about efficacy, taking into account adverse effects. Global outcome scores are also well validated, and are accepted by regulatory agencies.[8]

In RA joint pain, swelling, assessments of physical function, blood acute phase response and patient and physician global assessments have been combined, in various ways, to give composite measures of disease activity. Most widely used are the American College for Rheumatology percentage criteria - ACR20 referring to 20% improvement in several disease measures - and the disease activity score (DAS) – which relies on a formula using several disease measures.[15]

2.2 Non-Steroidal Anti-inflammatory Drugs

NSAIDs, by inhibiting the enzyme cyclooxygenase (COX) and reducing prostaglandin production, diminish inflammation and pain. Currently three forms of COX are known: COX-1, found in most normal tissues including the gastrointestinal tract, kidneys and platelets; COX-2 found particularly in the kidney, brain, bone and reproductive organs but increased substantially in any tissue with inflammation or injury and; COX-3, a newly identified COX found in highest concentrations in the brain and heart and possibly one of many isoenzymes of COX-1.[18]

At present only COX-1 and COX-2 are clinically relevant. COX-1 is regarded as a housekeeping enzyme responsible - through prostaglandins and thromboxane A2 - for physiological functions such as helping to protect gut mucosal integrity and vascular homeostasis by aiding vasoconstriction and platelet activation and clumping. COX-2 appears to be a more important mediator in inflammation and thus a key factor in arthritis pain. This is supported by clinical studies of COX-2 selective NSAIDs that reduced arthritis pain equally as well as non-selective NSAIDs, while reducing the risk of gut ulceration. However

concerns have been raised that suppression of COX-2 may inhibit beneficial inflammation and cause harm; for example, COX-2 expression found with *Helicobacter pylori* infection of the stomach, and gastric ulcers, may contribute to tissue repair.[19,20]

2.3 Classification of NSAIDs

Aspirin inhibits COX-1 irreversibly in platelets; these cells, lacking a nucleus, are unable to re-synthesize COX-1. In higher doses aspirin is an effective analgesic but also inhibits COX-1 in the gut and increases the risk of upper GI bleeding and ulcers greatly. The risk of GI haemorrhage with low dose aspirin (<325 mg per day), used for preventing strokes and heart attacks, is 2.5% compared with 1.4% for placebo (odds ratio 1.7).[21]

NSAIDs differ in their ability to inhibit COX-2 and can be separated according to the ratio of COX-1: COX-2 inhibition. Such distinctions relate, to some extent, to clinical GI toxicity seen in observational studies (Table 1). But, higher doses used in practice - or a longer plasma half-life – may make laboratory assessments of COX-2 selectivity irrelevant; at least for older NSAIDs.[22] Older NSAIDs are, mostly, not selective for COX-2 although some, like diclofenac, are similar to celecoxib and meloxicam in laboratory assays of COX-2 selectivity. Drugs, safer for the gut, tend to be given to people at higher risk of bleeding, and tend to have less favourable results in observational studies than might be expected.[23] As there is no consensus on the best way of defining COX-2 selectivity an emphasis on overall clinical advantage for each drug seems sensible.[24,25]

Table 1: Ranks for cyclooxygenase selectivity and gastrointestinal safety compared

	Ranking*	
Drug	***COX-2 to COX-1***	***GI safety***
Rofecoxib	1	-
Etodolac	2	-
Celecoxib	3	-
Diclofenac	4	2
Meloxicam	5	-
Ibuprofen	6	1
Piroxicam	7	8
Naproxen	8	6
Sulindac	9	5
Fenoprofen	10	3
Indomethacin	11	7
Ketoprofen	12	9
Flubiprofen	13	-
Aspirin†	14	4
Azapropazone	-	10

* Ranks for COX-2 selectivity are based on in vitro analysis using the whole blood assay. Ranks shown were derived from the hierarchy reported by Warner et al.[22] Ranks for GI safety shown according to the hierarchy reported by Henry et al.[26] † Dose range for aspirin not described by Henry et al.

2.4 COX-2 selective NSAIDs

The licensed doses for OA and RA for each of the COX-2 selective NSAIDS considered in this report are summarised in the table below.

Table 2: Recommended and maximum daily dose for COX-2 selective NSAIDs

Drug	OA		RA	
	Recommended	Maximum	Recommended	Maximum
Celecoxib	200mg	400mg	200-400mg	400mg
Etodolac	600mg	600mg	600mg	600mg
Etoricoxib	60mg	60mg	90mg	90mg
Meloxicam	7.5mg	15mg	15mg	15mg
Rofecoxib	12.5mg	25mg	25mg	25mg
Valdecoxib	10mg	20mg	10mg	20mg

Source: BNF 46 (September 2003)

2.5 Toxicity of NSAIDs

2.5.1 Gastrointestinal disorders

Anorexia, heartburn, nausea, dyspepsia, diarrhoea and abdominal pain are common symptoms in the general population and often lead to consultation in primary care. Five to ten percent of the population seek advice from a GP for dyspepsia and 1% is referred to hospitals.[27,28] Use of NSAIDs increases the likelihood of dyspeptic symptoms, and of using drugs for dyspepsia[29] – so, up to 26% of NSAID users take drugs for dyspepsia or to prevent peptic ulcers in community studies.[3]

Dyspeptic symptoms occur in 4.8% of NSAID treated patients compared with 2.3% on placebo, in randomised trials (which are likely to include healthier subjects) and are the most common reason for cessation of therapy.[30] Dyspeptic symptoms are especially common with indomethacin and piroxicam and with higher doses of NSAIDs; but seem to be equally common with COX-2 selective and non-selective drugs, with prolonged use,[31] and are a poor predictor of peptic ulcers. Half of those investigated for dyspepsia have a normal endoscopy, 15% gastro-oesophageal reflux disease (GORD), 25% peptic ulcers and 2% malignancies. Endoscopic abnormalities are more likely in people over 45 years of age.[32,33]

Serious UGI events such as perforation or bleeding from gastric or duodenal ulcers occur in up to 2% of NSAID users with an estimated 2000 deaths annually in the UK.[34] Bleeding and perforation are often not heralded by symptoms[35] and ulcers seen at endoscopy occur in over a quarter of people taking ibuprofen and other non-selective NSAIDs, but less commonly with COX-2 selective NSAIDs.[36] Endoscopic lesions are a poor surrogate for upper gut bleeding or perforation: there is only limited data linking ulcers on endoscopy with these complications. This may be because the gut mucosa adapts to noxious insults: such as NSAIDs.[37] There are also indications that NSAIDs may cause ulcers, bleeding, inflammation, and scarring in the small intestine and colon although, in contrast to upper GI bleeding, such events are much less common.[38]

2.5.2 Predictors of serious GI toxicity

Current NICE guidance[2] does not recommend routine use of COX-2-selective NSAIDs but gives situations in which they may be preferred to non-selective NSAIDs, and others in which COX-2 selective drug use would be inappropriate. A brief commentary on current NICE guidance is given below.

- *People are aged 65 years or above.*
  Age is a continuous risk factor; thresholds for use at specific ages are, therefore, arbitrary and depend on appropriate judgements. Relative risks for each decade, from 50 years, rise from 1.8 (compared with those under 50) in the fifties to 9.2 over the age of 80 years.[39]
- *For people with a past history of peptic ulcer*.
  History of a peptic ulcer confers a higher risk of bleeding from the upper gut for NSAID users (COX-2 selective or otherwise), and non-users.[40] Relative risks: rofecoxib 5.2, naproxen 13.5.[41]
- *For people with other serious illnesses.*
  Current guidance is rather imprecise and cites additional co-morbidity including cardiovascular disease, renal or hepatic impairments, diabetes and hypertension. Data on these factors are limited and potentially unreliable;[42] however serious disability, for example from RA, is linked with a higher risk of upper GI bleeding.[41]
- *For people also taking anticoagulants.*
  Very high rates of GI haemorrhage have been reported for people using warfarin and NSAIDs; relative risks exceed 6.0.[43,44]
- *For people also using corticosteroids*.
  A consistently higher risk is noted for steroid users but it is unclear whether this is because steroids tend to be used in sicker individuals, especially in RA. Relative risks vary between 2 to 6.[41,43]
- *For people using NSAIDs for prolonged periods.*
  Since both OA and RA are incurable conditions, and assuming that an individual gains sustained benefit from an NSAID, use is likely to be prolonged. On this basis many patients with RA and OA would qualify for COX-2 selective agents from the outset.[45] The risk at a particular time point appears similar, regardless of the duration of prior NSAID use;[40] but, cumulative risk is likely to be greater with longer use. Some studies have indicated a higher risk of complications earlier during treatment[46] and the CLASS study showed that GI events were rare with diclofenac after 3 months of treatment but continued to accrue with celecoxib.[47,48]
- *Not for use with GI protective agents in order to reduce adverse effects.*
  A report from the Canadian Coordinating Office for Health Technology also does not recommend the routine use of COX-2 selective inhibitors and gastro-protective agents, such as proton pump inhibitors (PPIs), as a way of reducing GI toxicity.[49] However, experience is that gastro-protective agents are often used with the goal of reducing dyspeptic symptoms – using pragmatic approaches, and allowing continued use of an NSAID, where there is worthwhile benefit - not necessarily to reduce UGI bleeds or ulcers.[49,50] UGI symptoms or use of gastro-protective agents does appear to be linked, modestly, to higher rates of GI complications (RR 1.8).[41]
- *Not for use with concomitant aspirin*
  Low dose aspirin, alone or combined with COX-2 selective or with non-selective NSAIDs, increases the risk of endoscopic ulcers[51] and complications of ulcers;[52] perhaps to a greater extent with non-selective NSAIDs. However, large enough trials

have not been done, so far, to determine whether COX-2 selective agents should be preferred to non-selective NSAIDs in aspirin users.

2.5.3 Preventing gastrointestinal toxicity due to NSAIDs

PPIs such as omeprazole and lansoprazole; misoprostol, a prostaglandin analogue; and double doses of H2 receptor antagonists (H2RA): (equivalent to ranitidine 300 mg twice daily); all reduce the risk of NSAID induced gastric and duodenal ulcers (detected on endoscopy).[53] Standard doses of H2RAs (equivalent to ranitidine 150 mg twice daily) reduce the risk of duodenal ulcers but not gastric ulcers: the latter are a more important problem with NSAIDs: so, standard doses of H2RAs should not be used for preventing ulcers. Lansoprazole reduces the risk of ulcer complications in people who had developed ulcer complications, and who had *H. pylori* infection, whilst taking low dose aspirin.[54] Only one study, the MUCOSA trial, has investigated the role of prophylactic drug therapy (misoprostol 800 ug per day), used with NSAIDs, to prevent ulcer complications.[55] In MUCOSA the risk of ulcer complications was 0.57% with misoprostol and variety of NSAIDs compared with 0.95% for placebo with NSAIDs; but 10% of patients on misoprostol had diarrhoea compared with 4% on placebo.

Direct comparisons of gastro-protective agents show that omeprazole and misoprostol are superior to standard dose ranitidine for preventing NSAID induced gastric ulcers (omeprazole also prevents duodenal ulcers).[49] Again, more people given misoprostol withdrew because of abdominal pain and diarrhoea. Lansoprazole was equally effective at 15 or 30 mg[56] and omeprazole at 20 or 40 mg, in these trials.[57]

A COX-2 selective NSAID (celecoxib) was compared against diclofenac and omeprazole (20 mg) in people with arthritis who had experienced a bleeding ulcer, in a recent randomised trial. The probability of further bleeding was similar with either approach - around 6% over 6 months. Many patients in this study had other illnesses: over 20% had abnormal renal function, at entry, and over 20% more than one previous episode of ulcer bleeding.[58] Six percent of patients developed renal failure (creatinine > 200umol per litre). It is questionable whether some of these patients should have received any NSAID at all.

2.5.4 Helicobacter pylori and NSAIDs

The two most important factors related to peptic ulcer disease are *H. pylori* infection and NSAIDs; although the proportion of ulcers associated with neither of these is increasing,[59] and the proportion attributed to aspirin now exceeds that due to NSAIDs, in some studies.[60] It might be assumed that NSAIDs and *H. pylori*, together, magnify ulcer risk. This is unclear. Studies are inconsistent: some show that *H. pylori* infection reduces NSAID risk, perhaps because *H. pylori* increases prostaglandins;[60,61] others, that NSAIDs increase risk only in people with *H. pylori* infection who have not previously had NSAIDs.[59] Post hoc analysis of the VIGOR and CLASS studies, in which COX-2 selective NSAIDs were compared with other NSAIDs and evidence of *H. pylori* infection was sought, shows no clear relationship between signs of infection and ulcer complications.[41,62]

2.5.5 Cardiovascular and renal toxicity of NSAIDs

Non-selective NSAIDs that inhibit COX-1 have anti-platelet effects similar to aspirin but, because inhibition is reversible, are unreliable at inhibiting vascular thromboses.[63] Increased COX-2 expression, seen in tissue inflammation, may help maintain patent blood vessels, by limiting the effects of platelet activation. This is suggested by studies showing that COX-2

inhibitors reduce the production of prostacyclin, an important vasodilator and inhibitor of platelet clumping.[19,64] These laboratory data and the occurrence of more cardiovascular events in RA patients treated with rofecoxib compared with naproxen raised concerns about the cardiovascular safety of COX-2-selective NSAIDs.[65,66] Ibuprofen - but not diclofenac - antagonises the effect of aspirin and it has been suggested that it too may be hazardous in people at increased cardiovascular risk.[63] This has not, in general, been substantiated in observation studies of people with myocardial infarctions.[67,68]

Prostaglandins control renal blood flow, glomerular filtration rate, and salt and water excretion by the kidney. NSAIDs may cause oedema, hypertension, renal failure and exacerbate heart failure in susceptible individuals. Both COX-1 and COX-2 are important in regulating renal blood flow and COX-2-selective NSAIDs do not have any advantages over non-selective agents in terms of renal toxicity or hypertension. Care is needed with NSAIDs, of all classes, in people on anti-hypertensives, the elderly and others at risk of renal diseases.[69]

2.5.6 Other adverse effects

A variety of other adverse effects such as skin rashes including photosensitivity, allergic reactions, mouth ulcers, headaches, and tinnitus may occur with NSAIDs. Newer COX-2-selective NSAIDs (*coxibs*) belong to three distinct chemical classes: aryl methyl sulphones, including rofecoxib and etoricoxib; aryl sulphonamides, including celecoxib and valdecoxib; and carboxylic acids, including lumiracoxib. Sulphonamides commonly cause skin reactions – sometimes severe and life-threatening - which might account for more skin rashes seen with celecoxib and valdecoxib, than with other NSAIDs.[48,70]

In about 10% of cases, asthma may be aggravated by NSAIDs and aspirin. Reports suggest that COX-2 selective NSAIDs may be safer in aspirin-sensitive asthmatics than non-selective NSAIDs.[71] NSAIDs, including COX-2 selective drugs, may also exacerbate inflammatory bowel diseases.[72]

2.6 Use of NSAIDs in osteoarthritis and rheumatoid arthritis

Guidelines for OA management recommend analgesics, other than NSAIDs, are tried first, for pain.[73] However, as NSAIDs are more efficacious than paracetamol in OA trials, NSAIDs may be considered as initial therapy, if they were to be as safe[74] – and especially as most people are familiar with the effects of paracetamol. In practice patients sometimes only use NSAIDs for brief periods, perhaps for short-lived exacerbations of pain and many choose not to use any regular medication at all. Analyses of NSAID prescribing patterns in primary care indicate that patients frequently switch NSAIDs and often also use a gastro-protective agent.[75,76] This probably reflects the difficulties of pain management in some cases.

Experts do not recommend NSAIDs as sole therapy in RA since other drugs may reduce the risk of joint damage.[77] Patients with RA are twice as likely as patients with OA to experience complications of NSAIDs: perhaps because of greater levels of disability, co-morbidity or concomitant steroid use.[77] In practice, effective disease management with DMARDs may allow cessation or reduction in use of NSAIDs and steroids but some patients remain dependent on full doses of NSAIDs for many years.

2.7 Current use of NSAIDs

Prescribing of NSAIDs in primary care in England has shown little change over the past 5 years: the key change is an increase in use of COX-2-selective inhibitors; such that nearly a quarter of all NSAID prescriptions are for COX-2-selective NSAIDs and these drugs account for one half of all NSAID costs.[4] Diclofenac, ibuprofen, and naproxen, in that order are the most widely prescribed non-selective NSAIDs; prescribing volumes for diclofenac have increased slightly in recent years whilst prescribing for ibuprofen has declined.

The most recent data from the Prescription Pricing Authority indicates that rofecoxib is the most frequently prescribed COX-2 selective agent.[4] The indications for use of NSAIDs cannot be ascertained from this data but primary care surveys show, unsurprisingly, use of NSAIDs for a wide variety of indications. Audits of routine practice indicate that adherence to NICE guidance is poor particularly in terms of underutilisation of COX-2 selective agents in relevant circumstances but also use in patients not meeting guidance.[45,78] Overall it appears that strict adherence to current NICE guidance could lead to a substantial increase in the use of COX-2 selective NSAIDs.[45]

3 REVIEW OF PREVIOUS SYSTEMATIC REVIEWS ON COX-2 SELECTIVE NSAIDS

A number of published systematic reviews have reported on the efficacy and safety of COX-2 selective NSAIDs in patients with RA or OA. A review of these previous systematic reviews was therefore undertaken.

Several systematic reviews were identified from searches (see Appendix 2). Reviews were included if they fulfilled the following criteria:

- Reported a search strategy;
- Addressed one or more of the COX-2 selective NSAIDs drugs included in this report;
- Reported results numerically, (either in the form of a qualitative or quantitative (e.g. meta-analysis) synthesis.

In additional to traditional systematic reviews, a number of 'pooled analyses' were identified, many of which appeared to use individual patient data from trials.[79-111] These pooled analyses tended to provide little or no detail of trial search methods and criteria for selection of included trials and often failed to identify individual trials clearly. Thus these pooled analyses were judged to be open to major bias and were therefore excluded from this review.

Twenty English language systematic reviews meeting our inclusion criteria were found. [112-131] Two foreign language systematic reviews were not included.[132,133] Three aspects of these reviews were assessed in detail:

- Characteristics i.e. drug(s) examined,
- Trials included, patient population & outcomes assessed;
- Quality of the review; results of the review for key efficacy and safety outcomes, where possible in the form of a pooled numerical mean estimate and 95% CI.

A detailed overview of the characteristics, quality and findings of the included systematic reviews is provided in Appendix 1.

In summary, the findings of this review of existing systematic reviews is as follows:

- Many systematic reviews of the safety and efficacy of COX-2 selective NSAIDs have been published.
- The findings of these studies are remarkably consistent despite differences in quality, methods, and inclusion criteria.
- COX-2 selective NSAIDs were, in general, superior to placebo and had comparable efficacy to non-selective NSAIDs for RA and OA.
- COX-2 selective NSAIDs and placebo had similar rates of withdrawal due to adverse effects (including withdrawals due to GI symptoms).
- Compared with placebo some reviews suggested that COX-2 selective NSAIDs had similar rates of ulcers on endoscopy and PUBs although data are limited and there are concerns about the overall quality of reviews.
- Compared with non-selective NSAIDs reviews showed that selective NSAIDs had a reduced incidence of withdrawal due to adverse effects including GI adverse effects, ulcers on endoscopy and PUBs.

- Reviews suggested an increased risk of cardiovascular events with COX-2 selective NSAIDs.
- More recent and better quality systematic reviews also suggest important differences in safety for COX-2 selective NSAIDs related to dose, treatment duration and comparator non-selective NSAID.

4 CLINICAL EFFECTIVENESS

4.1 Methods

4.1.1 Protocol

This systematic review was undertaken in accord with the protocol published on the NICE website in November 2003. The methods for the identification of previous systematic reviews and meta-analyses are discussed in Section 3 and Appendix 1.

4.1.2 Search Strategy

The following sources were searched:

- Bibliographic databases: Cochrane Library (CENTRAL) 2003 Issue 4, MEDLINE (Ovid) 1966-October 2003, MEDLINE in Process & Other Non-Indexed Citations (Ovid) 4 & 11 November 2003 and EMBASE (Ovid) 1980 – October 2003. Index and text words representing the drug names were combined with terms for osteoarthritis and rheumatoid arthritis. A filter to identify clinical trials was incorporated as appropriate (See Appendix 2, pg 194, for full details)
- Internet sites of European Agency for the Evaluation of Medicinal Products (EMEA) and the Food and Drug Administration (FDA)
- Citations of relevant studies
- Contact with experts
- Invited pharmaceutical company submissions to NICE (both 2004 and 2000)

Because of the broader inclusion criteria of this review relative to the previous assessment report undertaken by NICE, databases were searched from their inception date for all drugs. Searches were not restricted by language. Industry submissions were also searched for both published and unpublished studies.

4.1.3 Inclusion and exclusion criteria

Studies were included if they met the following criteria:

- Study design: RCTs with duration of treatment ≥ 2 weeks (no restriction on patient numbers).
- Population: Patients with OA or RA; other forms of arthritis are excluded
- Intervention: COX-2 selective NSAIDs (i.e. celecoxib, rofecoxib, meloxicam, etodolac, etoricoxib, and valdecoxib) with or without concomitant medication. Trials including licensed and supra-licensed doses were considered.
- Comparator: Placebo, non-selective NSAIDs, or direct comparisons between COX-2 selective NSAIDs

The following categories of studies were excluded: dose-finding studies of COX-2 selective NSAIDs without a comparator; trials published only as abstracts (pharmaceutical companies were contacted to seek unpublished data in full) and trials that included only sub-therapeutic doses of COX-2 selective NSAIDs.

Based on these inclusion criteria, study selection was carried out independently by two reviewers. Disagreements were resolved by discussion. A third reviewer (PJ) was consulted when disagreements persisted after discussion. Agreement on study selection between

reviewers was judged to be 'good' (weighted Cohen's kappa: 0.78, 95% CI: 0.74 to 0.82). Reviewers were not blinded to any features of the report including authorship; however, inclusion and exclusion decisions were made prior to detailed scrutiny of results.

4.1.4 Data extraction strategy

Data from included trials were extracted by one reviewer using a standard data extraction form and independently checked by another reviewer. Results were extracted, where possible, for the intention to treat population as raw numbers plus any summary measures with standard deviations, confidence intervals and *P-values*. Discrepancies were resolved by discussion.

Full trial reports were given primacy over published trial reports and, where possible, the published trial report results were cross-checked.

4.1.5 Quality assessment strategy

The methodological quality of included studies was assessed on the basis of randomisation, adequate concealment of randomisation, level of blinding, use of intention-to-treat-analysis, and description of loss to follow up. An overall quality score (Jadad) was assigned to each study. Quality was assessed by a single reviewer and checked by a second. Disagreements were resolved by discussion, with reference to a third party where necessary.

4.1.6 Data reporting and synthesis

The population characteristics, interventions and methodological quality of all included studies, and for each COX-2 selective NSAID, were tabulated.

The following outcomes were selected for data synthesis:

Effectiveness

OA trials: patient's assessment of pain due to arthritis assessed on a VAS or WOMAC sub-scale for pain where the former was not available; patient global assessment of response to therapy or disease status where the former was not available; and withdrawals due to lack of efficacy.

RA trials: patient's assessment of VAS pain due to arthritis (or WOMAC pain subscale where the former was not available); ACR-20; patient global assessment of response to therapy or disease status where the former was not available; and withdrawals due to lack of efficacy.

Tolerability outcomes

For OA and RA trials: total adverse events; GI-specific adverse events; withdrawals due to adverse events; withdrawals due to GI-specific adverse events; and all withdrawals (for any reason).

Safety outcomes

For OA and RA trials: endoscopically-confirmed GI ulcers; complicated UGI events (POBs); symptomatic UGI ulcers and complicated UGI events combined (PUBs); myocardial infarction; and serious cardiovascular thrombotic events.

Given the policy-basis of this report, the reporting and discussion of evidence focuses on the benefits and harms of COX-2 selective NSAIDs relative to non-selective NSAIDs.To reflect this, in the results tables, placebo trials results are 'greyed out' and not discussed in the text of the report.

Standard meta-analytic methods were used to pool data. Binary outcomes were expressed as relative risks and pooled using the Mantel-Haenszel method. For continuous outcomes, the mean difference between baseline and follow group was compared between pairs of treatment groups. Mean differences were pooled as weighted mean differences, weighted for variance. Where statistically significant heterogeneity was indicated (i.e. $P<0.10$) outcomes were pooled using the DerSimonian Laird random effects approach and heterogeneity explored using meta-regression.[134,135] Where trials reported only a mean variance at baseline and follow up, the baseline-follow up mean difference variance was imputed assuming an intercorrelation coefficient of 0.50.[136]

For the purposes of economic modelling we sought an overall pooled estimate of effect of each COX-2 drug. Trials outcome data were therefore pooled across trials, drug doses, follow up and arthritis indication. The reasons for this were first, the effect of COX-2 selective drugs appears to be equivalent across arthritis indications;[126,131] and second pilot meta-regression analyses for celecoxib showed that the duration of trial follow up, dose and arthritis indication were not independent predictors the effect of drug efficacy and safety (see Appendix 3, pg 206). However, where possible, pooled results stratified by drug dose and arthritis indication are also presented. Where trials randomised patients to more than one dose of COX-2 or NSAID, results from the eligible arms were combined into a single estimate for inclusion in the meta-analysis.

Summary statistics are presented with 95% confidence intervals throughout. Statistically significant results ($P\leq0.05$) are *italicised* in results table. All analyses were undertaken using Microsoft Excel and Stata versions 7 and 8.

4.2 Results

4.2.1 Quantity of research available

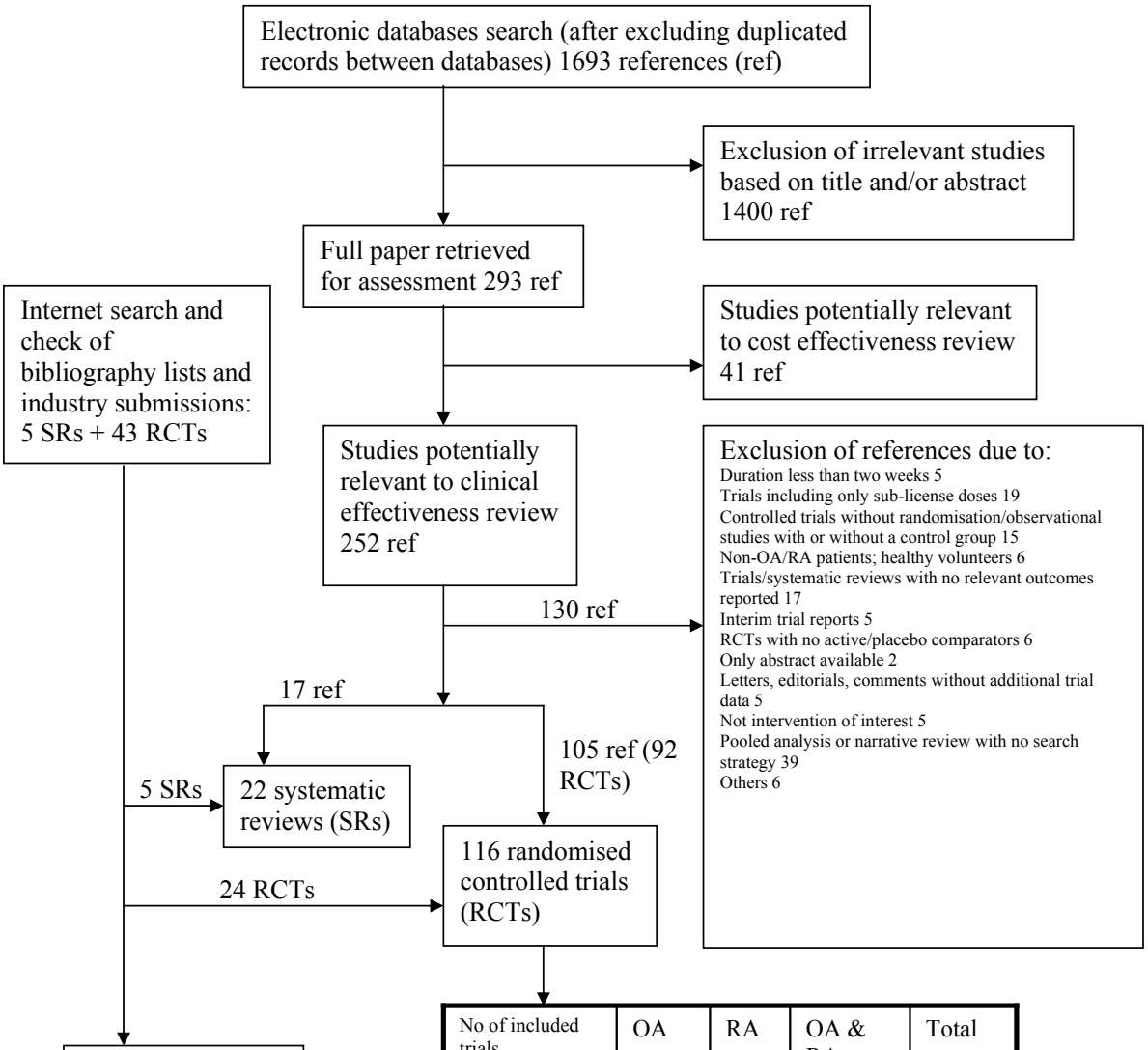
Sensitive rather than specific search strategies were used and therefore a large number of publications were identified. Many of these could be excluded on the basis of title or abstract and after detailed review of full papers and identification of duplicate publication a total of 116 relevant RCTs were identified: 29 trials for etodolac; 16 trials for meloxicam; 35 trials for celecoxib; 25 trials for rofecoxib; 11 trials for valdecoxib and 7 trials for etoricoxib (see Figure 1). Within these trials there were seven trials that compared two COX-2 selective drugs directly: six trials compared rofecoxib to celecoxib; and one trial compared rofecoxib to valdecoxib.

Some RCTs, that met inclusion criteria, were not included as they were not available either as full publications or as full reports from industry at the time of this systematic review (see Table 3).

Table 3: COX-2 selective NSAIDs – summary of number of identified randomised controlled trials

	Included RCTs	Additional RCTs identified	Comments
Etodolac	29	0	
Meloxicam	16	11*	*RCTs available as abstract or synopsis form at time of this review
Celecoxib	35	9*	*Company identified 9 RCTs. Trial reports not available at time of this review
Rofecoxib	25	5*	*Poster presentations or part trial report of RCTs available at time of this review
Valdecoxib	11	0	
Etoricoxib	7	3*	*Poster presentations or part trial report of RCTs available at time of this review
Total	**116**	**28**	

Figure 1: Flow diagram for identified trials



No of included trials	OA	RA	OA & RA	Total
Etodolac	24	5	0	29
Meloxicam	12	4	0	16
Celecoxib	24[a]	4	7	35[a]
Rofecoxib	21[b]	4	0	25[b]
Valdecoxib	6[c]	4	1	11[c]
Etoricoxib	4	2	1	7
Total	84	23	9	116

a: 6 of the trials had rofecoxib arm; b: 6 of the trials had celecoxib arm and one had valdecoxib arm; c: one trial had rofecoxib arm

4.3 Celecoxib

4.3.1 Description of included trials

35 trials of celecoxib met the inclusion criteria. Three trials comparing celecoxib with rofecoxib (without additional placebo or NSAID comparator) will be described in section 4.9. A detailed summary of the characteristics of the remaining 32 trials is given in Appendix 5, pg 210, and summarised in Table 4, pg 34.

A large proportion of trials were of a relatively short duration (i.e. <3 months), only two trials having follow up of 6-months or longer. The median sample size of trials was 626 patients. The two major trials were CLASS and SUCCESS-I, trial each recruiting over 5,000 patients.

CLASS
CLASS is a double blind RCT that included patients with OA and RA with the aim of comparing the tolerability and safety of Celecoxib at supra-licensed dose (400mg twice daily, n=3987) to diclofenac (75mg twice daily, n=1996) and ibuprofen (1.2g twice daily, n=1985). This study has been highly controversial and the published findings, in 1999, challenged because the published report described 26-week outcome data that claimed superiority of celecoxib (PUBs 32/3987) against pooled data for ibuprofen and diclofenac group (PUBs 51/3981: RR: 0.63, 95% CI: 0.40 to 0.97).
This study comprised two study protocols designed prospectively to combine results into a single study that pooled celecoxib data.[137] The primary end-point for CLASS was to compare the incidence of clinically significant upper GI events (which refers to upper GI bleeding, perforation or obstruction). The sponsors justified publication of the 6-month data on the grounds that this was a clinically relevant time point and allowed comparison with the MUCOSA study which studied misoprostol with NSAIDs for prevention of UGI toxicity. Pfizer also claimed that disproportionate withdrawal of patients treated with ibuprofen or diclofenac, due to the development of GI symptoms but not serious GI events, during the first 6 months contributed to fewer significant UGI events in these groups (described as 'informative censoring'.[137] These arguments were refuted by the FDA and the final study data was made available on their website. At 52 weeks PUBs in the celecoxib group (46/3987) was not significantly different to the combined ibuprofen and diclofenac group (65/3981) (RR: 0.71, 95% CI: 0.49 to 1.03).

SUCCESS-I
This was a 12-week double blind RCT of OA patients undertaken across 1142 centres in 37 countries. The primary objective was to compare the tolerability and safety of licensed doses of celecoxib (100 or 200mg twice daily, n=8840) with naproxen (500mg twice daily, n=914) or diclofenac (50mg twice daily, n=3510). Although efficacy was assessed in this trial, outcome means (and not measures of variance) were only available for individual countries or continents. It was therefore not possible to include efficacy data in a meta-analysis of all trials. However, the pattern of efficacy results indicated that both doses of celecoxib had similar efficacy to non-selective NSAIDs. The tolerability and safety results of this trial were included in our meta-analyses.

Patient characteristics
Most trials involved patients with OA (19 studies), usually hip or knee. Seven trials included both RA and OA patients and four trials only RA patients. The average age of patients across trials ranged from 50 to 74 yrs with 35% to 89% of patients being female.

Details of baseline risk characteristics were either not reported or not collected in many trials, for example current steroid use, *H. pylori* status or previous peptic ulcers. Where such information was reported, included patients were of functional class I and III, 5% to 45% had experienced a previous GI ulcer, 7% to 21% were taking low dose aspirin and over 75% of patients were chronic NSAIDs users.

Study interventions
Most trials assessed licensed celecoxib doses (200 mg/day, n=18 & 400mg per day n=15), six trials also included supra-license doses of celecoxib (>400mg per day). Fifteen studies compared celecoxib to placebo and 18 compared celecoxib with non-selective NSAIDs: naproxen 500mg twice daily (n=8), diclofenac 75mg twice daily (n=11), and ibuprofen 800mg three times daily (n=3).

4.3.2 Assessment of the quality of included trials

A median Jadad score across trials of 5 indicated that trials were generally of 'very good' quality (see Table 4, pg 34). A detailed summary of the quality of included trials is provided in Appendix 6, pg 254.

It was possible, because of access to full trial reports for most celexcoxib trials, to assess methodological aspects of their trial design in detail. The majority of trials were properly randomised (21/30), were double blind (30/30), stated intention-to-treat analysis (28/30), and reported small losses to follow up (<5%) (23/30). A small number of trials (14/30) reported concealment details.

Although trial quality was good, a large proportion of patients withdrew (20 to 50%) due to adverse events, lack of efficacy or for other reasons. Withdrawal often differed between drugs and, in general, was lower for celecoxib than non-selective NSAIDs. This meant that the duration of drug exposure was unequal across randomised groups leading to a potential bias against celecoxib although appropriate expression of data, for example as events per 100 patient years of exposure in CLASS allowed meaningful comparisons.

Table 4: Characteristic and quality of included celecoxib randomised controlled trials

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Celecoxib	Placebo	NSAID	Efficacy+	Safety+		
Simon 1998a, Pfizer Study 013[138]	OA (knee)	80mg per day (40mg bd) (n=71) 200mg per day (100mg bd) (n=73) 400mg per day (200mg bd) (n=76)	n=73	-	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	-		
Bensen 1999, Pfizer Study 020 [139,140 141]	RA	100mg per day (50mg bd) (n=218) 200mg per day (100mg bd) (n=217) 400mg per day (200mg bd) (n=222)	n=220	Naproxen 1000mg per day (500mg bd) (n=216)	Pain (VAS), Functional status (WOMAC), Patient's global assessment, Withdrawal due to lack of efficacy	Withdr events, Ulcer (sympto and obs Dyspep infarcti cardiov Total A AE, Wi GI AE		
Williams 2000, Pfizer Study 060 [142]	OA (knee)	200mg per day (100mg bd) (n=231) 400mg per day (200mg bd) (n=223)	n=232	-	Pain (VAS), Functional status WOMAC, Patient's global assessment, Withdrawal due to lack of efficacy	Withdr events, Dyspep infarcti cardiov Total A		
Goldstein 2001b[143]**, SUCCESS-1, Pfizer Study 096 (Pfizer 2004 submission)**	OA (knee, hip, hand)	200mg per day (100mg bd) (n=4421) 400mg per day (200mg bd) (n=4429)	-	Diclofenac 100mg per day (50mg bd) (n=3510), Naproxen 1000mg per day (500mg bd) (n=914)	Pain (VAS), Functional status Composite WOMAC change, Patient's global assessment of arthritis, Withdrawal due to lack of efficacy	Ulcer (Gastic l ('diagn Total P obstruc Myocar Total ca thromb severe, Withdr		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Celecoxib	Placebo	NSAID	Efficacy+	Safety+		
Kivitz 2001, Pfizer Study 054 [144]	OA (hip)	200mg per day (100mg bd) (n=216) 400mg per day (200mg bd) (n=207) 800mg per day (400mg bd) (n=213)	n=218	Naproxen 2000mg per day (1000mg bd) (n=207)	Pain (VAS), Functional status WOMAC composite+, Patient's global assessment, Withdrawal due to lack of efficacy	Withdr events, Dyspep infarcti severe, Withdr		
McKenna 2001b, Pfizer Study 152 [145]	OA (knee)	200mg per day (200mg od) (n=63)	n=60	Rofecoxib 25mg per day (25mg od) (n=59)	Pain (VAS), Functional status WOMAC, Withdrawal due to lack of efficacy	Withdr events, Dyspep infarcti cardiov Total A AE, Wi GI AE		
McKenna 2001a, Pfizer Study 118 [146]	OA (knee)	200mg per day (100mg bd) (n=199)	n=201	Diclofenac 150mg per day (50mg tds) (n=200)	Pain (VAS), Functional status (WOMAC), Patient's global assessment, Withdrawal due to lack of efficacy	Withdr events, AE sev		
Pfizer Study 021 (2000/1 submission)	OA (knee)	100mg per day (50mg bd) (n=252) 200mg per day (100mg bd) (n=239) 400mg per day (200mg bd) (n=233)	n=242	Naproxen 1000mg per day (500mg bd) (n=226)	Pain (VAS), Functional Status (WOMAC), Patient's global assessment efficacy, Patient's global assessment tolerability, Withdrawal due to lack of efficacy	Ulcer – Gasrroc Dyspep infarcti cardiov Total A AE, Wi AE, Wi GI AE		
McKenna 2002, Pfizer Study 042 [147]	OA (hip, knee)	200mg per day (100mg bd) (n=346)	-	Diclofenac 100mg per day (50mg bd) (n=341)	Patient's global assessment, Withdrawal due to lack of efficacy	Total w Dyspep due to (		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Celecoxib	Placebo	NSAID	Efficacy+	Safety+		
Pfizer Study 047 (2000/1 submission)	OA (knee)	50mg per day (25mg bd) (n=101) 200mg per day (100mg bd) (n=101) 800mg per day (400mg bd) (n=99)	n=101	-	Pain (VAS), Functional status (WOMAC), Patient's global assessment of arthritis, Patients global assessment of tolerability, Withdrawal due to lack of efficacy	Total w Dyspep infarcti cardiov Total A AE, Wi GI AE		
Williams 2001, Pfizer Study 087 [148]	OA (knee)	200mg per day (100mg bd) (n=243) 400mg qd (n=231)	n=244	-	Pain (VAS), Functional status WOMAC, Patient's global assessment, Withdrawal due to lack of efficacy	Total w Myocar Total ca thromb severe, Withdr adverse Withdr		
Suarez-Otero 2002, [149]	OA (knee, hand, hip)	200mg per day (100mg bd) (n=40)	-	Diclofenac-cholestyramine 280mg per day (140mg bd) (n=41)	Pain (VAS)	Withdr events,		
Gibofsky 2003, Pfizer Study 003 [150]	OA (knee)	200mg per day (200mg od) (n=189)	n=96	Rofecoxib 25mg per day (25mg od) (n=190)	Pain (VAS), Functional status (WOMAC), Patient's global assessment, Withdrawal due to lack of efficacy	Withdr events, Dyspep severe,		
Hawel 2003, [151]	OA (hip)	200mg per day (100mg bd) (n=74)	-	Dexibuprofen 800mg per day (400mg bd) (n=74)	Pain (VAS), Functional status (WOMAC), Patient's global assessment efficacy, Patients global assessment tolerability, Withdrawal due to lack of efficacy	Withdr events, Total A		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Celecoxib	Placebo	NSAID	Efficacy+	Safety+		
Pincus 2004a PACES-a, Pfizer Study 010 [152,153]	OA (hip, knee)	6 wks x1: 400mg per day (200mg bd) (n=181)	n=172	Acetaminophen 4000mg per day (1000mg qds) (n=171)	WOMAC target joint	NR		
Sowers 2002, CRESCENT, Pfizer Study 002 (Pfizer 2004 submission)	OA (hip, knee)	200mg per day (200mg od) (n=136)	-	Rofecoxib 25mg per day (25mg od) (n=138), Naproxen 1000mg per day (500mg bd) (n=130)	Pain (VAS), Functional status WOMAC, Patient's global assessment, Withdrawal due to lack of efficacy	Total w Dyspep infarcti cardiov Total A		
Pincus 2004b PACES-b, Pfizer Study 249 [152]	OA (hip, knee)	400mg per day (200mg bd) (n=189)	n=182	Acetaminophen 4000mg per day (1000mg qds) (n=185)	WOMAC target joint, MDHAQ VAS pain VAS GI distress	NR		
Simon 1998b, Pfizer Study 012 [138]	RA	80mg per day (40mg bd) (n=81) 400mg per day (200mg bd) (n=82) 800mg per day (400mg bd) (n=82)	n=85	-	Patient's global assessment, Withdrawal due to lack of efficacy	NR		
Emery 1999, Pfizer Study 041 [154]	RA	400mg per day (200mg bd) (n=326)	-	Diclofenac 150mg per day (75mg bd) (n=329)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdr events, def: >= gastodu Myocar Total c thromb severe,		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Celecoxib	Placebo	NSAID	Efficacy+	Safety+		
Simon 1999, Pfizer Study 022 [155,156]	RA	200mg per day (100mg bd) (n=240) 400mg per day (200mg bd) (n=235) 800mg per day (400mg bd) (n=218)	n=231	Naproxen 1000mg per day (500mg bd) (n=500)	Pain (VAS), Functional status (WOMAC), Patient's global assessment, Withdrawal due to lack of efficacy	Withdr events, Ulcer (gastodu (clinica Dyspep infarcti cardiov Total A AE, Wi GI AE		
Pfizer Study 023 (2000/1 submission)	RA	400mg per day (200mg bd) (n=228) 800mg per day (400mg bd) (n=218)	n=221	Naproxen 1000mg per day (500mg bd) (n=217)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Total w Dyspep infarcti cardiov Total A AE, Wi AE		
Silverstein 2000, CLASS study, Pfizer Study 035/102 [157,158] [159-161] [162,163]	RA & OA	800mg per day (800mg od) (n=3987)	-	Diclofenac 150mg per day (150mg od) (n=1996), Ibuprofen 2400mg per day (2400mg od) (n=1985)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdr events, Sympto Gastroc Duoden severe, to GI A		
Goldstein 2001, Pfizer Study 062 [164]	RA & OA (73%)	400mg per day (200mg bd) (n-270)	-	Naproxen 1000mg per day (500mg bd) (n=267)	Patient's global assessment arthritis, Withdrawal due to lack of efficacy	Withdr events, Ulcer e Gastroc (clinica Dyspep infarcti cardiov Total A AE, Wi		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Celecoxib	Placebo	NSAID	Efficacy+	Safety+		
						GI AE		
Pfizer Study 071 (2000/1 submission)	OA or RA	400mg per day (200mg bd) (n=366)	-	Diclofenac 150mg per day (75mg bd) (n=387), Ibuprofen 2400mg per day (800mg tds) (n=346)	Patient's global assessment, Withdrawal due to lack of efficacy	Total w Gastod Ulcer (sympto Myocar Total c thromb severe, Withdr		
Chan 2002[165]	OA (87%), & RA (2%) & other (11%)	400mg per day (200mg bd) (n=144) + placebo	-	Diclofenac 150mg per day (75mg bd) + Omeprazole 20mg per day (20mg od) (n=143)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdr events, Total A due to		
Pfizer Study 105 (2004 submission)	RA & OA (site not stated)	200mg per day (100mg bd) (n=332)	-	Diclofenac 100mg per day (50mg bd) (n=334)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdr events, Ulcer (score>7 Duoder Total A AE, Wi GI AE		
Pfizer Study 106 (2004 submission)	RA & OA (site not stated)	200mg per day (100mg bd) (n=63)	-	Diclofenac 100mg per day (50mg bd) (n=62)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdr events, Ulcer (score>7 Duoder severe, Withdr		
Pfizer Study 107 (2004 submission)	RA & OA (site not stated)	200mg per day (100mg bd) (n=45)	-	Diclofenac 100mg per day (50mg bd) (n=44)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdr events, Ulcer (score>7 Dyspep		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Celecoxib	Placebo	NSAID	Efficacy+	Safety+		
						severe, Withdr		
Pfizer Study 210 (2003) USA (24 centres)	OA (site not stated)	200mg per day (200mg od) (n=145)	n=78	Naproxen 1000mg per day (500mg bd) (n=144)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Total w PUB, D Myocar Total ca thromb		
Pfizer Study 211 (2003) USA (31 centres)	CiC removedOA (site not stated)	200mg per day (200mg od) (n=127)	n=62	Naproxen 1000mg per day (500mg bd) (n=129)	Pain (VAS), Withdrawal due to lack of efficacy	Total w cardiov Total A due to (		
Pfizer Study 209 (2003) International Multicentre	OA (site not stated)	200mg per day (200mg od) (n=127)	n=67	Naproxen 1000mg per day (500mg bd) (n=128)	Patient's global assessment, Withdrawal due to lack of efficacy	Total w Dyspep infarcti Withdr		
Pfizer Study 216 (2002) Japan (85 centres)	OA (site not stated)	200mg per day (100mg bd) (n=382)	n=192	Ioxoprofen 1800mg per day (60mg tds) (n=385)	Patient's global assessment, WOMAC pain, Withdrawal due to lack of efficacy	Total w Dyspep infarcti Withdr		

4.3.3 Assessment of celecoxib efficacy

Efficacy results are summarised in Table 5, pg 42 (placebo-only information given in grey shaded cells).

Patients' assessment of arthritis pain
There was no statistically significant improvement in pain over non-selective NSAIDs. These results held for OA and RA patients, different celecoxib doses and choice of NSAID comparator.

Patient's assessment of global efficacy
There was no significant difference in global efficacy to compartor NSAIDs. This result held for OA and RA patients, celecoxib doses and also the choice of NSAID comparator.

ACR-20 responder
ACR-20 response was reported in three trials of RA patients. Celecoxib was no better than comparator NSAIDs. These effects were consistent for different celecoxib doses and choice of NSAID comparator.

Withdrawals due to lack of efficacy
There was no difference in withdrawal rates on comparing celecoxib with non-selective NSAIDs. These results held for OA and RA patients, celecoxib dose and choice of NSAID comparator.

Table 5: Summary of efficacy results of celecoxib versus placebo and NSAIDS

	Placebo				NS			
	VAS Pain difference Mean (95% CI)	**Global efficacy difference Mean (95% CI)**	**ACR 20 RR (95% CI)**	**Withdrawals due to lack of efficacy RR (95% CI)**	**VAS Pain difference Mean (95% CI)**	**Global efficacy difference Mean (95% CI)**		
200mg/day	*-9.7 (-11.8 to -7.8)**	*-0.36 (-0.40 to -0.29)*	*1.38 (1.13 to 1.69)*	*0.39 (0.28 to 0.53)**	-1.4 (-4.1 to 1.9)*	0.00 (-0.05 to 0.06)		
400mg/day	*-9.4 (-10.9 to -7.8)*	*-0.36 (-0.42 to -0.29)*	*1.64 (1.38 to 1.95)*	*0.44 (0.34 to 0.58)**	2.3 (-2.2 to 6.8)	-0.01 (-0.06 t 0.05)		
>400mg/day	*-11.6 (-16.6 to -6.6)**	*-0.39 (-0.48 to -0.29)*	*1.53 (1.28 to 1.82)*	*0.54 (0.47 to 0.62)**	-0.8 (-2.0 to 0.4)	-0.01 (-0.07 t 0.05)		
OA only	*-10.4 (-12.4 to –8.3) [15]*	*-0.37 (-0.51 to -0.21)* [8]*	*No trials*	*0.31 (0.21 to 0.47)* [8]*	1.73 (-1.24 to 4.70) [4]	0 (-0.05 to 0.07) [4]		
RA only	*-9.9 (-13.7 to –6.1) [3]*	*-0.32 (-0.45 to -0.20) [4]*	*1.54 (1.32 to 1.79) [3]*	*0.53 (0.44 to 0.65) [4]*	-0.1 (-3.6 to 3.4) [2]	-0.02 (-0.17 t 0.13) [4]		
All trials	***-10.6 (-12.1 to -8.5)* [18]***	***-0.35 (-0.45 to -0.25) [12]***	***1.54 (1.32 to 1.79) [3]***	***0.41 (0.33 to 0.52)* [11]***	**-0.42 (-2.4 to 1.6)* [14]**	**0 (-0.05 to 0.03) [15]**		

* heterogeneity P<0.01 & random effects model used; [ ]: N trials

4.3.4 Celecoxib tolerability

Adverse events

Adverse events were considered at two levels: all adverse events and GI-related adverse events (see Table 6, pg 44).

There were no statistically significant differences in overall and GI-specific adverse events compared to NSAIDs. There was evidence of significant heterogeneity across trials.

Withdrawals

Withdrawals were considered at three levels: withdrawal from the trials for any reason (including loss to follow up, lack of efficacy or adverse events); withdrawal due to adverse events, and withdrawal due to GI-specific adverse events (see Table 7, pg 45).

The proportion of GI-specific adverse events with celecoxib was lower than NSAIDs. However, withdrawal due to the reduction in all adverse events did not reach conventional levels of statistical significance for any reason. There was evidence of significant heterogeneity across trials such that withdrawals for an adverse event. Stratified analysis by celecoxib dose (see Table 7, pg 45) showed that the decrease in GI withdrawal with celecoxib was independent of celecoxib dose.

Table 6: Summary of adverse events for celecoxib versus placebo & NSAIDs

	Placebo **Relative risk (95% CI)** **[N trials]**	**NSAIDs** **Relative risk (95% CI)** **[N trials]**
All adverse events		
200mg per day	*1.07 (1.02 to 1.13) [13]*	*0.912 (0.89 to 0.95) [15]*
400mg per day	*1.12 (1.06 to 1.11) [10]*	0.96 (0.93 to 1.00) [9]
800mg per day	1.07 (0.38 to 1.16) [5]	1.00 (0.98 to 1.02) [4]
OA only	*1.06 (1.00 to 1.12) [13]*	*0.92 (0.89 to 0.96) [11]*
RA only	*1.13 (1.03 to 1.22) [4]*	1.00 (0.82 to 1.08) [4]
All trials	***1.03 (1.04 to 1.13) [17]***	**0.96 (0.91 to 1.01)* [21]**
All GI adverse events		
200mg per day	1.13 (0.94 to 1.36) [9]	*0.80 (0.64 to 0.91)* [9]*
400mg per day	1.40 (0.98 to 1.99) [8]	0.95 (0.81 to 1.11) [8]
800mg per day	*1.44 (1.20 to 1.75) [5]*	0.85 (0.71 to 1.00) [3]
OA only	1.15 (0.89 to 1.50) [7]	*0.77 (0.65 to 0.91) [4]*
RA only	1.15 (0.89 to 1.50) [4]	1.04 (0.80 to 1.33)* [4]
All trials	***1.30 (1.05 to 1.61)* [11]***	**0.90 (0.78 to 1.04)* [13]**

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

Table 7: Summary of withdrawals for celecoxib versus placebo & NSAIDs

	Placebo Relative risk (95% CI) [N trials]	**NSAIDs Relative risk (95% CI) [N trials]**
All adverse event withdrawals		
200mg per day	1.20 (0.93 to 1.516) [14]	*0.74 (0.64 to 0.94) [15]*
400mg per day	1.00 (0.51 to 1.97) [10]	1.00 (0.69 to 1.45)* [8]
800mg per day	*1.61 (1.14 to 2.88) [5]*	*0.91 (0.84 to 0.98) [4]*
OA only	1.00 (0.64 to 1.58)*[13]	*0.75 (0.62 to 0.92)* [10]*
RA only	1.61 (0.87 to2.98)* [4]	1.16 (0.68 to1.97)* [4]
All trials	**1.14 (0.76 to 1.69)* [17]**	**0.86 (0.73 to 1.00)* [21]**
All GI withdrawals		
200mg per day	1.38 (0.74 to 2.58) [5]	*0.35 (0.24 to 0.52) [7]*
400mg per day	1.54 (0.83 to 2.83) [4]	*0.48 (0.36 to 0.64) [7]*
800mg per day	2.27 (1.00 to 5.17) [2]	0.62 (0.35 to 1.10) [2]
OA only	1.51 (0.85 to 2.66) [5]	*0.39 (0.26 to 0.57) [3]*
RA only	CiC removed [1]	*0.38 (0.25 to 0.58) [2]*
All trials	**1.65 (0.97 to 2.79) [6]**	***0.45 (0.35 to 0.56) [11]***
All withdrawals		
200mg per day	*0.76 (0.61 to 0.95)* [12]*	1.03 (0.89 to 1.19)* [13]
400mg per day	*0.65 (0.52 to 0.81)* [8]*	0.94 (0.75 to 1.19)* [7]
800mg per day	*0.72 (0.61 to 0.84) [4]*	*0.94 (0.90 to 0.97) [3]*
OA only	*0.71 (0.59 to 0.86)* [13]*	1.05 (0.87 to 1.26)* [10]
RA only	0.60 (0.29 to 1.22) [2]	0.82 (0.68 to 1.00) [2]
All trials	***0.70 (0.39 to 0.83)* [15]***	**0.93 (0.84 to 1.05)* [18]**

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

4.3.5 Safety of celecoxib

The safety of celecoxib was evaluated by considering the development of endoscopic GI ulcers, clinical UGI events (PUBs), complicated UGI events (POBs), myocardial infarctions and serious cardiovascular thrombotic events (see Table 8, pg 46 and Table 9, pg 48).

Endoscopic ulcers

There was a statistically (RR: 0.32, 95% CI 0.23-0.47) significant decrease in endoscopically confirmed GI ulcers with celecoxib compared to non-selective NSAIDs. This decrease was consistent across celecoxib doses and type of arthritis. There was evidence of significant heterogeneity across trials.

Clinical UGI events (PUBs)

Significantly fewer patients experienced PUBs on celecoxib compared to non-selective NSAIDs (RR: 0.64, 0.46-0.89; NNT: 376, 95% CI 251-1230; see Figure 3, pg 47). There were too few trials to examine the effect of type of arthritis, follow up time and choice of NSAID on the effect of celecoxib on PUBs relative to comparator NSAIDs.

Complicated UGI events (POBs)

Five trials compared rates of POBs for celecoxib and NSAIDs (naproxen, ibuprofen or diclofenac). The pooled risk of POBs was reduced with celecoxib (RR: 0.56, 0.32-0.69; NNT: 653, 422-7178; see Figure 1, pg 31) and stratification by celecoxib dose indicated that POBs were independent of celecoxib dose.

Myocardial infarctions and serious cardiovascular thrombotic events
An almost two-fold increase in the relative risk of myocardial infarction was seen with celecoxib compared to NSAIDs (RR: 1.87, 1.06-3.30; NNH: 773, 293-11214; see Figure 4, pg 48). This increased risk, appeared to be independent of celecoxib dose (see Table 9, pg 48).

Table 8: Summary of endoscopic GI ulcers and serious GI events (PUBs and POBs) for celecoxib versus placebo or NSAIDs

	Placebo **Relative risk (95% CI) [N trials]**	**NSAID** **Relative risk (95% CI) [N trials]**
Endoscopic GI ulcers		
200mg per day	1.49 (0.66 to 3.34) [2]	*0.29 (0.10 to 0.54) [3]*
400mg per day	1.78 (0.69 to 4.59) [2]	*0.31 (0.20 to 0.48) [5]**
800mg per day	CiC removed [1]	CiC removed *[1]*
OA only	CiC removed [1]	CiC removed *[1]*
RA only	CiC removed [1]	*0.22 (0.15 to 0.33) [2]*
All trials	**1.70 (0.83 to 3.45) [2]**	***0.32 (0.23 to 0.47) [6]****
POBs*		
200mg per day	0.45 (0.07 to 2.97) [2]	0.33 (0.09 to 1.24) [2]
400mg per day	CiC removed [1]	*0.21 (0.05 to 0.95) [3]*
800mg per day	No trials	CiC removed [1]
OA only	CiC removed [1]	*0.23 (0.06 to 0.83) [2]*
RA only	No trials	CiC removed [1]
All trials	**0.30 (0.04 to 2.17) [2]**	***0.56 (0.32 to 0.96) [3]***
PUBs*		
200mg per day	No trials	CiC removed [1]
400mg per day	No trials	CiC removed [1]
800mg per day	No trials	CiC removed [1]
OA only	No trials	CiC removed *[1]*
RA only	No trials	No trials
All trials	**No trials**	***0.64 (0.46 to 0.89) [2]***

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

Figure 2: Risk of POBs with celecoxib (all doses) vs NSAIDs (all drugs) [figure CIC]

CiC removed

Figure 3: Risk of PUBs with celecoxib (all doses) vs NSAIDs (all drugs) [figure CIC]

CiC removed

Table 9: Summary of serious CV events for celecoxib versus placebo or NSAIDs

	Placebo **Relative risk (95% CI) [N trials]**	**NSAID** **Relative risk (95% CI) [N trials]**
MI		
200mg per day	0.75 (0.17 to 3.33) [3]	4.48 (0.83 to 24.1) [2]
400mg per day	1.69 (0.52 to 5.45) [5]	*2.87 (1.02 to 8.06) [7]*
800mg per day	1.45 (0.28 to7.40) [3]	2.19 (0.38 to 12.5) [3]
OA only	0.91 (0.22 to 3.70) [3]	3.70 (0.86 to 15.87) [3]
RA only	1.36 (0.29 to 6.41) [3]	2.18 (0.47 tp 10.08) [4]
All trials	**1.09 (0.39 to 3.08) [6]**	***1.87 (1.06 to 3.30) [9]***
Serious CV thrombotic events		
200mg per day	1.20 (0.23 to 4.37) [3]	0.92 (0.42 to 2.01) [2]
400mg per day	0.92 (0.31 to 2.74) [6]	1.07 (0.55 to 2.11) [6]
800mg per day	1.00 (0.14 to 7.03) [2]	CiC removed [1]
OA only	0.89 (0.28 to 2.82) [5]	0.91 (0.47 to 1.76) [3]
RA only	CiC removed [1]	2.57 (0.33 to 20.03) [2]
All trials	**0.78 (0.27 to 2.22) [6]**	**0.99 (0.54 to 1.79) [6]**

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

Figure 4: Risk of MI with celecoxib (all doses) vs NSAIDs (all drugs) [figure CIC]

CiC removed

4.3.6 Subgroup analyses

Subgroup analyses of endoscopic ulcers according to low-dose aspirin use, *H. Pylori* status, age (≤ 65 yrs vs >65yrs) and history of prior GI ulceration (refs) was done in six trials; and two large trials (CLASS and SUCCESS-I) did subgroup analyses of PUBs and POBs by low dose aspirin use. SUCCESS-I also presented MI rates in treatment groups stratified by low-dose aspirin use. No identified trials reported subgroup analysis based on use of anti-coagulants.

Endoscopic ulcers

Subgroup stratified pooled relative risks for endoscopically-detected ulcers with celecoxib compared to conventional NSAIDs are summarised in Table 10.

Table 10: Endoscopic ulcer for celecoxib vs non-selective NSAID by sub-groups

Subgroup [N trials]	Pooled events Celecoxib vs NSAID	Pooled relative risk (95% CI)**	Comparative relative risk & P-value+
H-pylori status			
Positive [5]	31/326 vs 82/337	*0.39 (0.27 to 0.57)*	1.56
Negative [5]	44/884 vs 161/788	*0.25 (0.18 to 0.34)*	P=0.211
Low dose aspirin			
User [5]	18/185 vs 44/164	*0.39 (0.23 to 0.66)*	1.18
Non user [5]	78/1596 vs 233/1347	*0.33 (0.18 to 0.63)**	P=0.678
Age			
≤ 65 yrs [5]	33/528 vs 104/430	*0.33 (0.19 to 0.59)**	1.06
> 65yrs [5]	64/1452 vs 178/1178	*0.31 (0.21 to 0.44)*	P=0.756
Prior GI ulcer			
Present [5]	28/263 vs 68/208	*0.42 (0.29 to 0.62)*	1.68
Not present [5]	69/1737 vs 223/1334	*0.25 (0.15 to 0.42)*	P=0.171
Steroids			
User [4]	16/378 vs 44/238	*0.25 (0.10 to 0.63)*	0.69
Non user [4]	58/877 vs 227/976	*0.36 (0.27 to 0.48)*	P=0.376

*Significant heterogeneity – pooled by random effects
**Relative risk celecoxib vs conventional NSAID
+Significance of comparative RR≠1.00

Relatively small numbers of events in these subgroups counsel caution when interpreting these data. Celcoxib significantly reduced endoscopic events compared to non-selective NSAIDs in each subgroup group pair.

PUBs and POBs

The subgroup stratified pooled relative risks PUBs and POBS with celecoxib compared to conventional NSAIDs are summarised in Table 11, pg 50.

Table 11: POBs and PUBs for celecoxib vs conventional NSAID by low dose aspirin use

Subgroup [N trials]	Pooled events	Pooled relative risk (95% CI)**	Comparative relative risk & P-value+
POBs			
User [2]	10/1134 vs 8/973	0.99 (0.39 to 2.50)	2.82
Non user [2]	9/11283 vs 27/7860	*0.35 (0.17 to 0.72)*	P=0.138
PUBs			
User [1]	CiC removed	CiC removed	CiC removed
Non user [1]	CiC removed	CiC removed	CiC removed

Low dose aspirin is suggestive of a reduction in celecoxib benefit on POBs and [CiC removed]. However, given the very small number of events observed in the trials, these data need confirmation.

Myocardial infarction
Subgroup analysis for low dose aspirin on MI rates from the SUCCESS-I trial are summarised in Table 12.

Table 12: MI for celecoxib vs conventional NSAID by low dose aspirin use

Subgroup [N trials]	Pooled events	Pooled relative risk (95% CI)**	Comparative relative risk & P-value+
MI			
User [1]	CiC removed	CiC removed	CiC removed
Non user [1]	CiC removed	CiC removed	CiC removed

CiC removed

4.3.7 Impact of concomitant gastroprotective agents

Only one trial comparing celecoxib to an NSAID plus a gastro-protective agent was identified. Chan and colleagues [165] compared diclofenac and omeprazole combined versus celecoxib alone in patients with arthritis who had suffered a recent GI haemorrhage on NSAIDs. The 6-month probability of recurrent bleeding was 4.5% and 5.6% for celecoxib and diclofenac-omeprazole group respectively (not statistically significant). The authors concluded that the two strategies for recurrent ulcer prevention were equivalent.

4.3.8 Summary

- 34 randomised controlled trials (RCTs) were included. Studies compared celecoxib (200 to 800mg/day) to either placebo or non-selective NSAIDs (naproxen or diclofenac).
- Celecoxib is of similar efficacy to non-selective NSAIDs for the symptomatic treatment of OA and RA.
- Celecoxib is associated with significantly fewer GI-related adverse events and related withdrawals compared to non-selective NSAIDs.
- Celecoxib is associated with significantly fewer endoscopic GI ulcers than non-selective NSAIDs. This benefit appears to be independent of low dose aspirin use, prior GI ulcer history, H. pylori-status and age although conclusions are based on limited data.
- Celecoxib is associated with significantly fewer clinical and complicated UGI events than non-selective NSAIDs. This benefit appears to be independent of concomitant low dose aspirin but this conclusion is based on small numbers and needs confirmation.
- In people with a recent UGI bleed celecoxib and diclofenac plus omeprazole may be equivalent, but this is based on a single trial and needs confirmation.
- [CiC removed].

4.4 Meloxicam

4.4.1 Description of included trials

Sixteen trials of meloxicam recruiting 22,886 patients met inclusion criteria. Full details of these trials are detailed in Appendix 5, pg 194 and summarised in Table 13, pg 54.

Two major trials, MELISSA and SELECT, recruited over 8,000 patients each. A majority (11/16) of trials were of short duration (< 3-months) and ranged from 2 weeks to 6-months.

MELISSA
This large international multicentre double-blind RCT was designed to assess the tolerability and safety of meloxicam 7.5 mg per day (half the maximum licensed dose; n=4,320 patients) compared with slow release diclofenac 100 mg per day (two-thirds the usual full dose; n=4,326) in OA over 28 days. MELISSA was powered to detect a 1% difference in adverse events. Because of limited reporting, the quality of MELISSA was judged to be only 'moderate' (i.e. Jadad score 3).

SELECT
SELECT was similar in design to MELISSA, except that meloxicam 7.5 mg per day (n=4635 patients) was compared with piroxicam 20 mg per day (two-thirds the maximum licensed dose; n=4336) in OA over 28 days. Again, because of limited reporting, the quality of MELISSA was judged to be only 'moderate' (i.e. Jadad score 3).

Patient characteristics
Most trials studied OA patients (12 trials) rather than RA patients (4 trials) with a mean age in the range 54 to 72 years and females 15% to 90%. Patient characteristics were often poorly reported but where reported 5% to 7% had experienced a previous GI ulcer. Usage of low dose aspirin and oral corticosteroids was not reported. It appeared that virtually all included patients were already taking NSAIDs at the time of recruitment.

Study interventions
Meloxicam at licensed doses (7.5mg or 15mg per day) was used in all trials and three trial also studied doses greater than 15 mg per day but in two of these trials data for 30mg per day were not reported (Linden, 1996; The Goei 1997). One trial provided data on meloxicam 22.5 mg per day (Furst and colleagues). Four trials compared Meloxicam to placebo, two of these trials being placebo only trials. Thirteen trials compared meloxicam to NSAIDs: diclofenac (6/13), piroxicam (4/13), narproxen (1/13) and nabumetone (2/13).

4.4.2 Assessment of the quality of included trials

The median Jadad score across trials was 3 indicating the trials were generally of 'moderate' quality (see Table 13, pg 54). A detailed summary of the quality of trials is provided in Appendix 6, pg 254.

Low quality scores were largely the result of poor reporting of methods. Very few trials provided details of randomisation (3/16) or concealment (0/16); most were double blind (14/16) and stated intention-to-treat analysis (15/16); and in four of six trials, where details were reported, there was a loss to follow of less than 5%. As with other COX-2 selective drugs, a potential source of the bias in these trials was the large proportion of withdrawals:

withdrawal in the non-selective NSAIDs arm of trials exceeded that of meloxicam although drug doses used are not directly comparable.

Table 13: Characteristic and quality of included meloxicam randomised controlled trials

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Meloxicam	Placebo	NSAID	Efficacy+	Safety+		
Carrabba 1995 [166,167]	RA	15mg per day (15mg od) (n=216)	-	Piroxicam 20mg per day (20mg od) (n=109+)	Patient's global assessment	Withdraw events, T Total AE		
Hosie 1996, BI Study 63 [168]	RA	7.5mg per day (7.5mg od) (n=169)	-	Diclofenac SR 100mg per day (100mg od) (n=167)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Total AE		
Linden 1996, BI Study 43 [169]	OA (hip)	15mg per day (15mg od) (n=129) 30mg per day (30mg od) (n=?)	-	Piroxicam 20mg per day (20mg od) (n=127)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (cli PUB, Tot		
Goei The 1997, BI Study 44 [170]	OA (knee)	15mg per day (15mg od) (n=128) 30mg per day (30mg od) (n=?)	-	Diclofenac SR 100mg per day (100mg od)	Patient's global assessment,	Withdraw events, U Dyspepia		
Hosie 1997, BI Study 45 [171]	OA (hip, knee)	15mg per day (15mg od) (n=306)	-	Piroxicam 20mg per day (20mg od) (n=149)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Total AE to GI AE		
Dequeker 1998, SELECT, BI Study 154 [172]	OA (knee, spine, hip, hand)	7.5mg per day (7.5mg od) (n=4320)	-	Piroxicam 20mg per day (20mg od) (n=4336)	Pain 100 mm VAS (on active movement), Pain 100 mm VAS (at rest), Patient's global efficacy, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (en confirme Total PU Myocardi Total car thrombot severe, T Withdraw		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Meloxicam	Placebo	NSAID	Efficacy+	Safety+		
Hawkey 1998, MELISSA, BI Study 153 [173]	OA (knee, spine, hip, hand)	7.5mg per day (7.5mg od) (n=4635)	-	Diclofenac SR 100mg per day (100mg od) (n=4688)	Pain 100 mm VAS - active movement, Pain 100 mm VAS - at rest, Patient's global efficacy, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (en surgical), symptom Total PU Total AE to GI AE		
Lund 1998, BI Study 42 [174,175]	OA (knee)	7.5mg per day (7.5mg od) (n=140) 15mg per day (15mg od) (n=134)	n=137	-	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Total AE		
Yocum 2000, BI Study 181 [176,177 178]	OA (hip, knee)	3.75mg per day (3.75mg od) (n=154) 7.5mg per day (7.5mg od) (n=154) 15mg per day (15mg od) (n=156)	n=157	Diclofenac 100mg per day (50mg bd) (n=153)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (cli Total AE Withdraw		
Chang 2001 [179]	OA (knee)	7.5mg per day (7.5mg od) (n=36)	-	Piroxicam 20mg per day (20mg od) (n=36)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (en or duodei Total AE		
Valat 2001 [180] **BI Study 94**	OA (lumbar spine)	7.5mg per day (7.5mg od) (n=117)	-	Diclofenac 100mg per day (100mg od) (n=112)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Total PU Myocardi Total car thrombot severe, T		
Xu 2002a [181]	OA (knee)	7.5mg per day (7.5mg od) (n=31)	-	Nabumetone 1000mg per day (1000mg od) (n=29)	Pain during activity (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Total AE to GI AE		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Meloxicam	Placebo	NSAID	Efficacy+	Safety+		
Wojtulewski 1996, BI Study 61 [182,183]	RA	7.5mg per day (7.5mg od) (n=199)	-	Naproxen 750mg per day (250mg tds) (n=180)	Pain (VAS), Patient's global assessment efficacy, Patient's global assessment tolerance, Withdrawal due to lack of efficacy	Withdraw events, U duodenal Total AE Withdraw		
Lemmel 1997, BI Study 35 [184,185]	RA	7.5mg per day (7.5mg od) (n=159) 15mg per day (15mg od) (n=162)	n=147	-	Pain (VAS), Patient's global assessment efficacy, Patient's global assessment tolerance, Withdrawal due to lack of efficacy	Withdraw events, U gastric/du (clinical) Total AE to GI AE		
Furst 2002, BI Study 183 [186,187]	RA	7.5mg per day (7.5mg od) (n=175) 15mg per day (15mg od) (n=184) 22.5mg per day (22.5mg od) (n=177)	n=177	Diclofenac 150mg per day (75mg bd) (n=181)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (cli PUB, Dy severe, T Withdraw		
Xu 2002b [188,189]	RA	15mg per day (15mg od) (n=59)	-	Nabumetone 1000mg per day (1000mg od) (n=61)	Patient's global assessment (disease status), Withdrawal due to lack of efficacy	Withdraw events, T Total AE to GI AE		

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4.4.3 Assessment of meloxicam efficacy

Efficacy results across trials are summarised in Table 14, pg 59.

Patient's assessment of arthritis pain
Meloxicam was inferior to non-selective NSAIDs for providing pain relief.

Patient's assessment of global efficacy
Meloxicam was no different than non-selective NSAIDs for global efficacy. These results were consistent across meloxicam doses and OA and RA patients.

ACR-20 responder
No included meloxicam trials reported ACR-20.

Withdrawals due to lack of efficacy
More people on meloxicam withdrew because of lack of efficacy compared with non-selective NSAIDs. Again, these results appeared to be consistent to OA and RA patients and across meloxicam doses.

Table 14: Summary of efficacy results of meloxicam versus placebo and NSAIDS

	Placebo				NS			
	VAS Pain difference Mean (95% CI)	**Global efficacy difference Mean (95% CI)**	**ACR RR (95% CI)**	**Withdrawals due to lack of efficacy RR (95% CI)**	**VAS Pain difference Mean (95% CI)**	**Global efficacy difference Mean (95% CI)**		
7.5mg/day	*-5.7 (-8.7 to –2.8) [1]*	-0.49 (-0.92 to 0.03) [2]	No trials	*0.59 (0.50 to 0.70) [4]*	*2.2 (1.2 to 3.1)* [7]	*-0.13 (-0.16 t -0.09)* [4]		
15mg/day	*-7.4 (-10.3 to –4.4) [3]*	-0.85 (-1.31 to 0.39) [2]	No trials	*0.54 (0.43 to 0.68) [4]*	-1.2 (-4.0 to 1.6) [4]	0.02 (-0.37 to 0.40) [3]		
22.5mg/day	*-9.9 (-15.7 to –4.1)*	*-0.87 (-1.42 to -0.32)*	No trials	*0.90 (0.53 to 0.89) [1]*	1.1 (-4.7 to 6.9) [1]	0.20 (-0.45 to 0.65) [1]		
OA only	*-5.3 (-10.5 to –0.1) [1]*	-0.50 (-1.20 to 0.20) [1]	No trials	*0.58 (0.44 to 0.77) [2]*	*1.7 (0.80 to 2.8)* [7]	-0.06 (-0.28 t 0.16) [3]		
RA only	*-7.2 (-10.2 to –4.3) [2]*	*-0.80 (-1.15 to -0.08)*	No trials	*0.60 (0.48 to 0.74) [2]*	1.4 (-1.9 to 4.2) [3]	0.03 (-0.44 to 0.51) [2]		
All trials	***-6.8 (-9.3 to –4.2) [3]***	***-0.65 (-1.14 to -0.14) [2]***	**No trials**	***0.59 (0.49 to 0.70)***	***1.7 (0.8 to 2.7)* [10]**	**-0.05 (-0.25 t 0.15) [5]**		

*random effects, heterogeneity P<0.01: [ ] N trials

4.4.4 Meloxicam tolerability

Adverse events

GI-specific and overall adverse events were comparable for meloxicam and placebo but statistically fewer people given meloxicam developed adverse events, overall and GI specific events, compared with non-selective NSAIDs in OA and RA. There was evidence of substantial heterogeneity in the level of GI-specific adverse events across meloxicam trials (see Table 15).

Withdrawals

Compared with placebo, there was some evidence that meloxicam increased the level of withdrawals due to all adverse events and GI-specific events was increased in meloxicam-treated patients, although this increase was not statistically significant. Meloxicam significantly reduced the level of both overall and GI-specific withdrawals compared to non-selective NSAIDs (see Table 16, pg 61).

Table 15: Summary of adverse events for meloxicam versus placebo & NSAIDs

	Placebo **Relative risk (95% CI) [N trials]**	**NSAIDs** **Relative risk (95% CI) [N trials]**
All adverse events		
7.5mg/d	1.07 (0.94 to 1.22) [4]	*0.86 (0.84 to 0.89) [10]*
15 mg/d	1.12 (0.98 to 1.326) [4]	0.97 (0.87 to 1.09) [5]
22.5 mg/d	1.13 (0.95 to 1.35) [1]	1.00 (0.85 to 1.18) [1]
OA trials	1.11 (0.94 to 1.31) [2]	*0.88 (0.81 to 0.95)* [10]*
RA trials	1.10 (0.96 to 1.27) [2]	0.99 (0.87 to 1.13)[3]
All trials	**1.10 (0.99 to 1.23) [4]**	***0.91 (0.84 to 0.99)*[13]***
All GI adverse events		
7.5mg/d	0.68 (0.41 to 1.10)* [4]	*0.29 (0.28 to 0.31)*[10]*
15 mg/d	0.86 (0.58 to 1.26)* [4]	***0.33 (0.21 to 0.51) [5]***
22.5 mg/d	*1.79 (1.42 to 2.27) [1]*	1.15 (0.99 to 1.94) [1]
OA only	0.68 (0.33 to 1.39)* [2]	*0.28 (0.22 to 0.37)*[10]*
RA only	0.91 (0.53 to 1.56)* [2]	*0.43 (0.31 to 0.61)* [3]*
All trials	**0.79 (0.55 to 1.12)* [4]**	***0.31 (0.24 to 0.39)* [13]***

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

Table 16: Summary of withdrawals for meloxicam versus placebo & NSAIDs

	Placebo Relative risk (95% CI) [N trials]	**NSAIDs Relative risk (95% CI) [N trials]**
All adverse event withdrawals		
7.5mg/d	1.21 (0.76 to 1.92) [2]	*0.60 (0.42 to 0.85)**[8]
15 mg/d	1.32 (0.84 to 2.08) [3]	0.96 (0.66 to 1.35) [4]
22.5 mg/d	1.07 (0.53 to 2.15) [1]	0.77 (0.40 to 1.45) [1]
OA only	1.25 (0.72 to 2.20) [2]	0.97 (0.62 to 1.52) [3]
RA only	1.20 (0.68 to 2.11) [1]	0.86 (0.53 to 1.40) [1]
All trials	**1.23 (0.82 to 1.84) [3]**	**0.92 (0.66 to 1.28) [4]**
All GI withdrawals		
7.5mg/d	1.40 (0.72 to 0.77) [4]	*0.60 (0.53 to 0.69)* [5]
15 mg/d	1.35 (0.69 to 2.65) [4]	0.76 (0.40 to 1.47) [3]
22.5 mg/d	1.18 (0.41 to 3.46) [1]	0.92 (0.38 to 2.11) [1]
OA only	2.01 (0.76 to 5.30) [2]	*0.60 (0.53 to 0.69)* [5]
RA only	1.04 (0.48 to 2.6) [2]	0.66 (0.41 to 1.06) [2]
All trials	**1.38 (0.76 to 2.51) [4]**	***0.61 (0.54 to 0.69)* [7]**
All withdrawals		
7.5mg/d	*0.57 (0.46 to 0.70)* [2]	*0.85 (0.76 to 0.96)* [6]
15 mg/d	*0.45 (0.35 to 0.57)* [2]	1.14 (0.83 to 1.52) [3]
22.5 mg/d	*0.51 (0.40 to 0.63)* [1]	1.11 (0.87 to 1.49) [1]
OA only	No trials	*0.80 (0.71 to 0.91)* [6]
RA only	*0.15 (0.10 to 0.21)* [1]	1.21 (0.94 to 1.55) [2]
All trials	***0.15 (0.10 to 0.21)* [1]**	***0.86 (0.77 to 0.96)* [8]**

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

4.4.5 Safety of Meloxicam

Few trials assessed the safety of meloxicam in terms of endoscopic GI ulcers, PUBs, POBs, MIs and serious cardiovascular thrombotic events (see Table 17 to Table 19, pgs 62-63).

Endoscopic GI ulcers

Meloxicam appeared to reduce the endoscopic ulcers compared to NSAIDs, although this difference failed to reach statistical significance.

Clinical UGI events (PUBs)

Overall there was no statistically significant difference in PUBs in patients treated with meloxicam compared to non-selective NSAIDs sub-group analysis in patients with OA was suggestive. There was evidence of a reduction in PUBs with meloxicam compared with non-selective NSAIDs in three of four trials in OA patients. In a trial in RA patients meloxicam caused more PUBs than diclofenac[186] but pooled data for all trials showed that differences in PUBs between meloxicam and non-selective NSAIDs were not statistically significant.

Complicated UGI events (POBs)

When meloxicam was compared with non-selective NSAIDs no statistically significant differences in PUBs were found.

Myocardial infarctions and serious cardiovascular thrombotic events
A total of only three events were reported across all included meloxicam trials providing insufficient data for meaningful comparisons. .

Table 17: Summary of endoscopic GI ulcers for meloxicam versus placebo or NSAIDs

	Placebo Relative risk (95% CI) [N trials]	**NSAID Relative risk (95% CI) [N trials]**
Endoscopic GI ulcers		
7.5 mg/d	No events [1]	0.50 (0.21 to 1.15)
15 mg/d	No trials	No trials
22.5 mg/d	No trials	No trials
OA only	No events [1]	0.56 (0.23 to 1.36) [4]
RA only	No trials	0.18 (0.01 to 3.74) [1]
All trials	**No events [1]**	**0.50 (0.21 to 1.15) [5]**

*****Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

Table 18: Summary of serious GI events for meloxicam versus placebo or NSAIDs

	Placebo Relative risk (95% CI) [N trials]	**NSAID Relative risk (95% CI) [N trials]**
PUBs		
7.5 mg/d	No trials	0.62 (0.32 to 1.20) [3]
15 mg/d	No trials	No trials
22.5 mg/d	No trials	No trials
OA only	No trials	*0.50 (0.25 to 0.98)* [3]
RA only	No trials	3.05 (0.17 to 56.3) [1]
All trials	**No trials**	**0.57 (0.30 to 1.08) [4]**
POBs		
7.5 mg/d	No trials	0.52 (0.26 to 1.05) [2]
15 mg/d	No trials	No trials
22.5 mg/d	No trials	No trials
OA only	No trials	0.52 (0.26 to 1.05) [2]
RA only	No trials	No trials
All trials	No trials	**0.52 (0.26 to 1.05) [2]**

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

Figure 5: Risk of POBs with meloxicam (all doses) vs NSAIDs (all drugs)

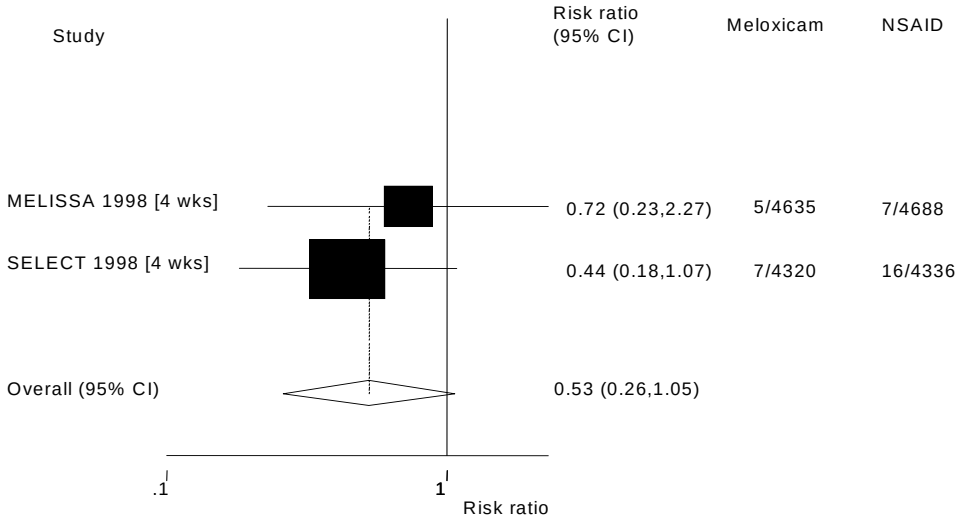


Figure 6: Risk of PUBs with meloxicam (all doses) vs NSAIDs (all drugs)

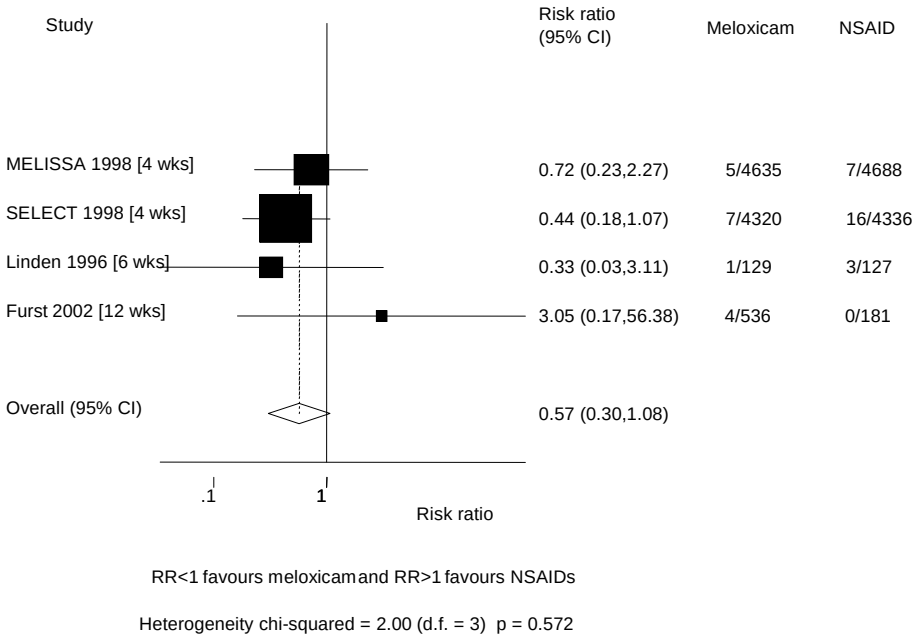


Table 19: Summary of serious CV events for meloxicam versus placebo or NSAIDs

	Placebo **Relative risk (95% CI) [N trials]**	**NSAID** **Relative risk (95% CI) [N trials]**
MI		
7.5 mg/d	0.32 (0.01 to 7.94) [1]	No trials+
15 mg/d	0.34 (0.01 to 8.29) [1]	No trials+
22.5 mg/d	No trials	No trials+
OA only	0.17 (0.01 to 4.08) [1]	No trials+
RA only	No trials	No trials+
All trials	**0.17 (0.01 to 4.08) [1]**	**No trials+**
Serious CV thrombotic events		
7.5 mg/d	No trials+	0.99 (0.05 to 15.7) [1]
15 mg/d	No trials+	No trials
22.5 mg/d	No trials+	No trials
OA only	No trials+	0.99 (0.06 to 15.9) [1]
RA only	No trials+	No events [4]
All trials	No trials+	**0.99 (0.06 to 15.9) [1]**

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis
+no events reported

4.4.6 Subgroup analyses

Low dose aspirin
No relevant trial data

H-pylori status
No relevant trial data..

Age
In SELECT, when subgroups of younger (≤65 yrs) and older (>65 yrs) male and female patients were analysed, in both, the incidence of GI adverse events was found to be lower with meloxicam than piroxicam. Actual numbers of events were not reported in these two age groups. Furst et al (2002) reported the rate of all adverse events to be lower in meloxicam than diclofenac for both patients aged ≤65 years (24.1% versus 29.4%) than patients aged >65 years (36.4% versus 42.1%).

Prior GI disease (GI ulcer)
In SELECT, fewer people who had a history of an ulcer developed GI adverse events when given meloxicam (7.5 mg) than piroxicam (20 mg per day): 91/236 (38.6%) compared with 95/212 (44.8%), respectively. This however was not statistically significant (P=0.180)

4.4.7 Impact of concomitant gastroprotective agents

No relevant trials identified.

4.4.8 Summary

- 17 RCTs were included. Studies compared meloxiocam (7.5 to 22.5 mg/day) to either placebo or non-selective NSAIDs (naproxen, diclofenac, nabumetone or piroxicam).
- Meloxicam is of similar or poorer efficacy than non-selective NSAIDs for the symptomatic treatment of OA and RA.
- Meloxicam is associated with significantly fewer GI-related adverse events and related withdrawals compared to non-selective NSAIDs.
- Meloxicam is associated with fewer endoscopic GI ulcers and clinical and complicated UGI events compared with non-selective NSAIDs although these differences were not statistically significance and differences may be accounted for by the choice of drug doses.
- There are insufficient trial events to assess the impact of meloxicam on the incidence myocardial infarction compared to non-selective NSAIDs.
- The GI protective effects of meloxicam appear to be consistent across age (≤ 65 yrs vs >65yrs) and prior history of GI events but no trial evidence that examined relative effect of meloxicam in patients taking concomitant low dose aspirin, anticoagulants or *H. pylori* status was found.
- No comparisons of meloxicam to non-selective NSAIDs with a gastro-protective agent were found.

4.5 Rofecoxib

4.5.1 Description of included trials

Twenty-five trials met inclusion criteria: seven trials that compared rofecoxib with another COX-2 selective NSAID; six with celecoxib; and one valdecoxib. In this section we describe the remaining eighteen trials that compared rofecoxib with a non-selective NSAID or placebo: full details are outlined in Appendix 6, pg 254.

The eighteen remaining trials recruited a total of 24,304 participants. The median sample size of the trials was 739 patients. The latrgest were VIGOR and ADVANTAGE that recruited over 8,000 and 5,000 patients, respectively. Most trials lasted for 3 months or less (13 out of 18) but some lasted as long as 1 year and four trials had an extension phase permitting observations up to 3 years after inception. The results from these trial extensions have not been included here, either because the initial randomisation was not maintained or, insufficient data were available.

VIGOR
This key multicentre international RCT studied the safety of rofecoxib 50 mg once daily (twice the licensed dose; n=4047) and naproxen 500 mg twice daily (n=4029) in RA patients. Patients, 80% of whom were female with a mean age of 58 years and had had RA for around 11 years, were treated for a median of 9 months. Over 50% of patients were also on oral corticosteroids, around 43% had evidence of *H. pylori* infection and around 8% had had a serious UGI event previously. PPIs were not permitted in this study but standard doses of H2RAs and antacids were allowed. Confirmed PUBs occurred with rofecoxib at a rate of 2.1 per 100 patient years (POB 0.6) and with naproxen at 4.5 per 100 patient years (POB 1.4). Myocardial infactions occurred in 0.1% of patients treated with naproxen compared with 0.4% of rofecoxib patients (RR 0.2, 95% CI 0.1 to 0.7). Many analyses including post-hoc comparisons of the rate of MIs in those eligible for aspirin, and those not, and reviews of the potential beneficial cardiovascular effects of naproxen have been done in the wake of this finding.

ADVANTAGE
This double-blind RCT compared cessation of treatment for GI adverse effects of rofecoxib 25 mg once daily (n=2799) with naproxen 500 mg twice daily (n=2787) in OA patients. It was conducted in primary care practices, principally in the USA. Use of medication to treat GI symptoms was allowed and was used as a secondary end point as were other safety outcomes, efficacy and quality of life. The quality of the study was judged to be high (Jadad score 5) but study duration was only 12 weeks. Discontinuations for GI symptoms occurred in 5.9% rofecoxib patients compared with 8.1% naproxen (p=0.005), 2 POB events occurred with rofecoxib compared with 9 for naproxen and 5 presumed MIs occurred with rofecoxib compared with 1 for naproxen.

4.5.2 Patient characteristics

Fourteen trials included patients with OA, mostly of hip or knee. Four trials included RA patients and none of the trials included both OA and RA patients. Mean age of the patients ranged from 52 to 83 years. More than 80% of patients had prior use of NSAIDs in thirteen of the trials. History of previous GI ulcers was not well reported. At least nine of the trials excluded patients on low-dose aspirin.

4.5.3 Assessment of the quality of included trials

Twelve of the eighteen studies were judged to be of good quality (Jadad score 5). Four trials scored 3-4 due to poorly reported randomisation and blinding methods. A small single-blind trial[190] had a Jadad score 1. Quality assessments of individual trials are summarised in Appendix 6, pg 254.

Table 20: Characteristics and quality of included rofecoxib randomised controlled trials

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Rofecoxib	Placebo	NSAID	Efficacy+	Safety+		
Ehrich 1999, MSD Study 010 [191]	OA (knee)	125mg per day (125mg od) (n=74) 25mg per day (25mg od) (n=73)	n=72	-	Pain (VAS), WOMAC physical function subscale, WOMAC stiffness subscale, Patient's global assessment of disease status, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (en), Ulcer (symptom Total PU Dyspepsi infarctior cardiovas Total AE		
Laine 1999, MSD Study 044/045 [192]	OA (not stated)	50mg per day (50mg od) (n=186) 25mg per day (25mg od) (n=195)	n=177	Ibuprofen 2400mg per day (800mg tds) (n=183)	Patient's global assessment of disease, Withdrawal due to lack of efficacy	Withdraw events, T Gastrodu Gastric U Ulcer, Ul symptom (clinical)		
Cannon 2000, MSD Study 035 [193,194]	OA (hip, knee)	12.5 mg per day (12.5mg od) (n=259) 25mg per day (25mg od) (n=257)	-	Diclofenac 150mg per day (50mg tds) (n=268)	WOMAC pain, WOMAC – Function subscale, WOMAC – stiffness subscale, Patient's global assessment of therapy response, Patient global assessment of disease status, Withdrawal due to lack of efficacy	Withdraw events (cl Withdraw adverse e withdraw or sympt or duoder PUB, My infarctior thromboc Total AE to GI AE		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Rofecoxib	Placebo	NSAID	Efficacy+	Safety+		
Day 2000, MSD Study 040 [195,196]	OA (hip, knee)	12.5 mg per day (12.5mg od) (n=244) 25mg per day (25mg od) (n=242)	n=74	Ibuprofen 2400mg per day (800mg tds) (n=249)	WOMAC pain, Patient global assessment of disease, Patient's global assessment of response to therapy, Withdrawal due to lack of efficacy	Withdraw 'clinical' Total wit (clinical Total AE		
Hawkey 2000, MSD Study 044/045 {402)	OA (not stated)	25mg per day (25mg od) (n=195) 50mg per day (50mg od) (n=193)	n=194	Ibuprofen 2400mg per day (800mg tds) (n=193)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer* (e AE		
Saag 2000a, MSD Study 033 [197]	OA (hip, knee)	12.5mg per day (12.5mg od) (n=219) 25mg per day (25mg od) (n=227)	n=69	Ibuprofen 2400mg per day (2400mg od) (n=221)	Pain (WOMAC), WOMAC – physical function, WOMAC – stiffness, Patient's global assessment of disease, Withdrawal due to lack of efficacy	Withdraw events, T Total car thrombot due to GI		
Saag 2000b, MSD Study 034 [197]	OA (hip, knee)	12.5mg per day (12.5mg od) (n=231) 25mg per day (25mg od) (n=232)	-	Diclofenac 150mg per day (150mg od) (n=230)	Pain 0-100 VAS, WOMAC – physical function, WOMAC – stiffness, Patient's global assessment of disease status, Patient's global assessment of response, Withdrawal due to lack of efficacy	Withdraw events, T Dyspepsi due to GI		
Acevedo 2001, Arthrotec trial, MSD Study 902 [198]	OA (not stated)	12.5mg per day (12.5mg od) (n=242)	-	Arthrotec (diclofenac 100mg; misoprostol 400mg per day) ((diclofenac 50mg; misoprostol 200mg) bd) (n=241)	Patient's global assessment (VAS 100mm), Withdrawal due to lack of efficacy	Withdraw events, T Dyspepsi cardiovas Total AE		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Rofecoxib	Placebo	NSAID	Efficacy+	Safety+		
Ehrich 2001, MSD Study 029 [199,200 201,202 203]	OA (hip, knee)	5mg per day (5mg od) (n=145) 12.5mg per day (12.5mg od) (n=149) 25mg per day (25mg od) (n=137) 50 mg per day (50mg od) (n=97)	n=145	-	Withdrawal due to lack of efficacy	Withdraw events		
Truitt 2001a, MSD Study 058 [204]	OA (hip, knee)	12.5mg per day (12.5mg od) (n=118) 25mg per day (25mg od) (n=56)	n=52	Nabumetone 1500mg per day (1500mg od) (n=115)	WOMAC pain sub-scale, WOMAC physical function, WOMAC stiffness sub-scale, Patient's global assessment of disease status, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (cli symptom Total AE		
Myllykangas-Luosujarvi 2002, MSD Study 901 [205]	OA (knee, hip)	Study 1 12.5mg per day (12.5mg od) (n=242) Study 2 12.5mg per day (12.5mg od) (n=229)	-	Naproxen Study 1 1000mg per day (500mg bd) (n=240) Study 2 1000mg per day (500mg bd) (n=233)	Pain on walking VAS, Functional status (e.g. WOMAC), Stiffness subscale (WOMAC), Patient's global assessment of disease status, Patient's global assessment of response to therapy, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (cli symptom Total PU Total AE		
Niccoli 2002 [190]	OA (hand, hip, knee)	25mg per day (25mg od) (n=30)	-	Diclofenac 150mg per day (150mg od) (n=30), Amtolmetin Guacyl 3600mg per day (1200mg tds) + 600mg per day (600mg od) (n=30)	Pain (e.g. VAS), Functional status (e.g. WOMAC), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, U def: >3M Withdraw		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Rofecoxib	Placebo	NSAID	Efficacy+	Safety+		
Lisse 2003, ADVANTAGE MSD Study 102/903 [206]	OA (knee, hand, hip, spine)	25mg per day (25mg od) (n=2785)	-	Naproxen 1000mg per day (1000mg od) (n=2772)	Patient's global assessment of disease status, Withdrawal due to lack of efficacy	Withdraw events, T Total PU obstructi infarctior thrombot events, W GI AE		
Kivitz 2004, MSD Study 085 [207]	OA (knee)	12.5mg per day (12.5mg od) (n=424)	n=208	Nabumetone 1000mg per day (1000mg od) (n=410)	Pain (e.g. VAS), Functional status (e.g. WOMAC), Patient's global assessment, Withdrawal due to lack of efficacy,	Withdraw adverse e withdraw (endosco (clinical Total PU obstructi		
Schnitzer 1999, MSD Study 068 [208]	RA	5mg per day (5mg od) (n=158) 25mg per day (25mg od) (n=171) 50 mg per day (50mg od) (n=161)	n=168	-	Pain - global (100 mm VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (en Ulcer (cli symptom Total PU Dyspepsi due to GI		
Bombardier 2000, VIGOR [209-211]	RA	50mg per day (50mg od) (n=4047)	-	Naproxen 1000mg per day (1000mg od) (n=4029)	Patient global assessment	Ulcer (cli symptom Myocard cardiac e due to GI		
Guesens 2002, MSD Study 097 [212]	RA	25mg per day (25mg od) (n=306) 50mg per day (50mg od) (n=286)	n=289	Naproxen 1000mg per day (1000mg od) (n=142)	Patient's global assessment of disease activity	Withdraw events, T Dyspepsi infarctior cardiovas Total AE to GI tole		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Rofecoxib	Placebo	NSAID	Efficacy+	Safety+		
Hawkey 2003, MSD Study 098/103	RA	50mg per day (50mg od) (n=219)	n=221	Naproxen 1000mg per day (500mg bd) (n=220)	Withdrawal due to lack of efficacy	Withdraw events, U Dyspepsi severe, T Withdraw		

4.5.4 Assessment of rofecoxib efficacy

The efficacy results across trials are summarised in Table 21, pg 74.

Patient's assessment of arthritis pain
Rofecoxib is of comparable efficacy to non-selective NSAIDs for pain relief in OA patients. One trial[212] compared rofecoxib 25 mg/day and 50 mg/day with naproxen in RA patients and was marginally favourable to naproxen but this was not statistically significant.

Patient's assessment of global efficacy
Rofecoxib of equivalent efficacy to non-selective NSAIDs but there was considerable heterogeneity across trials.

ACR-20 responder
Rofecoxib was equivalent to naproxen in two trials that reported this outcome.[208,212]

Withdrawals due to lack of efficacy
Similar proportions of patients treated with rofecoxib and non-selective NSAIDs withdrew from trials for lack of efficacy.

Table 21: Summary of efficacy results of rofecoxib versus placebo and NSAIDs

	Placebo				NSAID			
	VAS Pain difference Mean (95% CI)	**Global efficacy difference Mean (95% CI)**	**ACR-20 RR (95% CI)**	**Withdrawals due to lack of efficacy RR (95% CI)**	**VAS Pain difference Mean (95% CI)**	**Global efficacy difference Mean (95% CI)**		
12.5mg/day	*-14.88 (-15.18 to -14.58) [3]*	*-0.72 (-0.96 to -0.48) [1]*	No trials	*0.34 (0.25 to 0.45) [5]*	-0.77 (-4.21 to 2.68) [4] *	-0.06 (-0.22 to 0.10) [1]		
25mg/day	*-12.51 (-18.53 to -6.48) [4] **	*-0.81 (-1.36 to -0.26) [3] **	*1.41 (1.08 to 1.82) [1]*	*0.28 (0.19 to 0.41) [6]*	0.62 (-1.39 to 2.64) [4]	-0.06 (-0.38 to 0.25) [2] *		
>25mg/day	No trials	0.07(-0.14 to 0.28) [2] *	*1.55 (1.20 to 1.99) [1]*	*0.26 (0.17 to 0.40) [6]*	$ [1]	-0.07 (-0.28 to 0.14) [2] *		
OA only	*-14.74 (-17.93 to -11.54) [4] **	*-0.87 (-1.36 to -0.38) [3] **	Not applicable	*0.28 (0.22 to 0.35) [8]*	0.09 (-2.92 to 3.10) [6] *	-0.01 (-0.18 to 0.16) [3] *		
RA only	*-7.03 (-11.60 to -2.46) [1]*	$ [2]	*1.47 (1.17 to 1.86) [1]*	*0.44 (0.27 to 0.72) [2]*	$ [1]	0.02 (-0.02 to 0.06) [1]		
All trials	***-13.11 (-16.96 to -9.25) [5] **	***-0.87 (-1.36 to -0.38) [3] **	***1.47 (1.17 to 1.86) [1]***	***0.31 (0.25 to 0.38) [10]***	**0.09 (-2.92 to 3.10) [6] ***	**0.00 (-0.09 to 0.10) [4] ***		

* Heterogeneity P<0.01 & random effects model used; $ Insufficient data for meta-analysis; [ ]: N trials

4.5.5 Rofecoxib tolerability

Adverse events

Total adverse events with rofecoxib were similar to non-selective NSAIDs.

It was not possible to compare the risk of total GI adverse events between rofecoxib and placebo due to insufficient data. One trial [205] that compared rofecoxib 12.5 mg per day with naproxen 1000 mg per day found a significant reduction in the risk of GI adverse events with rofecoxib.

Table 22: Summary of adverse events for rofecoxib versus placebo & NSAIDs

	Placebo **Relative risk (95% CI)** **[N trials]**	**NSAIDs** **Relative risk (95% CI)** **[N trials]**
All adverse events		
12.5 mg	1.05 (0.91 to 1.22) [2]	0.98 (0.92 to 1.04) [4]
25 mg	*1.10 (1.03 to 1.18) [5]*	1.01 (0.96 to 1.06) [6]
> 25 mg	*1.10 (1.03 to 1.17) [5]*	1.01 (0.95 to 1.08) [4]
OA only	*1.07 (1.01 to 1.15) [5]*	1.00 (0.96 to 1.04) [7]
RA only	*1.10 (1.01 to 1.20) [2]*	0.98 (0.89 to 1.08) [2]
All trials	***1.08 (1.03 to 1.14) [7]***	**1.00 (0.96 to1.04) [9]**
GI adverse events		
12.5 mg	Not reported	*0.55 (0.42 to 0.73) [1]*
25 mg	Not reported	Not reported
> 25 mg	Not reported	Not reported
OA only	Not reported	*0.55 (0.42 to 0.73) [1]*
RA only	Not reported	Not reported
All trials	Not reported	***0.55 (0.42 to 0.73) [1]***

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

Withdrawals

Withdrawals from all adverse events, and GI adverse events, with rofecoxib were significantly more common with non-selective NSAIDs than rofecoxib. Fewer patients withdrew for any reason compared with non-selective NSAIDs, although differences did not reach statistical significance. Substantial heterogeneity was observed between trials for this outcome.

Table 23: Summary of withdrawals for rofecoxib versus placebo & NSAIDs

	Placebo **Relative risk (95% CI)** **[N trials]**	**NSAIDs** **Relative risk (95% CI)** **[N trials]**
All adverse event withdrawals		
12.5 mg	*1.94 (1.11 to 3.41) [5]*	*0.72 (0.59 to 0.89) [7]*
25 mg	1.27 (0.93 to 1.73) [9]	*0.69 (0.48 to 0.99) [10] **
> 25 mg	*1.86 (1.40 to 2.47) [7]*	0.84 (0.5 to 1.22) [5] *
OA only	*1.66 (1.23 to 2.23) [8]*	*0.75 (0.57 to 0.98) [11] **
RA only	1.41 (0.91 to 2.21) [3]	1.00 (0.90 to 1.10) [3]
All trials	***1.58 (1.24 to 2.02) [11]***	***0.78 (0.64 to 0.95) [14] ****
All GI withdrawals		
12.5 mg	0.79 (0.16 to 3.97) [1]	*0.58 (0.38 to 0.89) [4]*
25 mg	1.12 (0.61 to 2.06) [4]	*0.57 (0.34 to 0.95) [6] **
> 25 mg	*2.07 (1.18 to 3.63) [3]* †	*0.59 (0.36 to 0.96) [4] **
OA only	1.32 (0.70 to 2.46) [2]	*0.55 (0.34 to 0.88) [6] **
RA only	2.02 (0.91 to 4.46) [3]	*0.73 (0.64 to 0.85) [3]*
All trials	**1.56 (0.96 to 2.55) [5]**	***0.59 (0.45 to 0.78) [9] ****
All withdrawals		
12.5 mg	*0.57 (0.45 to 0.72 [3]*	0.91 (0.81 to 1.03) [6]
25 mg	0.69 (0.45 to 1.06) [6] *	0.72 (0.47 to 1.09) [8] *
> 25 mg	0.93 (0.60 to 1.42) [4] *	0.70 (0.44 to 1.12) [3]
OA only	0.72 (0.48 to 1.08) [6] *	0.76 (0.55 to 1.05) [10] *
RA only	0.71 (0.49 to 1.04) [1]	1.03 (0.96 to 1.10) [1]
All trials	**0.72 (0.51 to 1.02) [7] ***	**0.79 (0.57 to 1.08) [11] ***

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis
† one trial reported zero events in both arms.

4.5.6 Safety of rofecoxib

Endoscopic ulcers
Endoscopic ulcers were assessed in two OA studies [192,213] and one RA study[214] after up to 24 weeks treatment. Cumulative incidences of ulcers were calculated using survival analysis methods, taking into account of patient withdrawals. Between 5-7% of patients did not have a second endoscopy, after baseline, and were excluded from analysis. There was significantly fewer endoscopic gastroduodenal ulcers compared with non-selective NSAIDs.

Clinical UGI events (PUBs) and complicated UGI events (POBs)
Rofecoxib was associated with significantly fewer POBs (RR: 0.40, 0.23-0.70; NNT: 198, 155-397) and PUBs (RR: 0.43, 0.32-0.57; NNT: 81, 96-128) than with non-selective NSAIDs combined.

Myocardial infarctions and cardiovascular thrombotic events
Pooled results from three trials including VIGOR and ADVANTAGE indicated that rofecoxib significantly increases the risk of MI compared to non-selective NSAIDs (RR: 2.92, 1.29-6.60; NNH: 526, 180-3482) but that the occurrence of thromboembolic events is comparable.

Table 24: Summary of endoscopic GI ulcers and clinical and complicated UGI events (PUBs and POBs) for rofecoxib versus placebo or NSAIDs

	Placebo **Relative risk (95% CI)** **[N trials]**	**NSAID** **Relative risk (95% CI)** **[N trials]**
Endoscopic GI ulcers		
12.5 mg	No trial	No trial
25 mg	$ [2]	$ [2]
> 25 mg	$ [3]	$ [3]
OA only	$ [2]	$ [2]
RA only	$ [1]	$ [1]
All trials	**$ [3]**	$ **[3]**
POBs		
12.5 mg	†	0.34 (0.01 to 8.20) [1] ¶
25 mg	0.95 (0.13 to 6.87) [2]‡	*0.18 (0.04 to 0.77) [3]* †
> 25 mg	0.99 (0.14 to 7.02) [2] ¶	*0.41 (0.23 to 0.73) [3]*
OA only	0.68 (0.13 to 3.46) [3] †	0.24 (0.05 to 1.22) [3] ¶
RA only	†	*0.43 (0.24 to 0.77) [1]*
All trials	**0.68 (0.13 to 3.46) [3] ¶**	***0.40 (0.23 to 0.70) [4]*** **¶**
PUBs		
12.5 mg	†	0.39 (0.09 to 1.68) [2] †
25 mg	‡	*0.24 (0.09 to 0.65) [3]*
> 25 mg	2.97 (0.31 to 28.39) [2] †	*0.45 (0.33 to 0.61) [2]*
OA only	1.48 (0.06 to 35.88) [1] †	*0.32 (0.12 to 0.84) [3]* †
RA only	1.47 (0.06 to 35.90) [1] †	0.22 (0.03 to 1.51) [2] *
All trials	**1.47 (0.15 to14.09) [2] ¶**	***0.43 (0.32 to 0.57) [5]*** †

$ Meta-analysis not carried out as it was not possible to calculate RR or hazard ratio from survival analysis data
*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis
† one trial reported zero events in both arms. ¶ two trials reported zero events in both arms. ‡three trials reported zero events in both arms

Figure 7: Risk of POBs with rofecoxib (all doses) vs NSAIDs (all drugs)

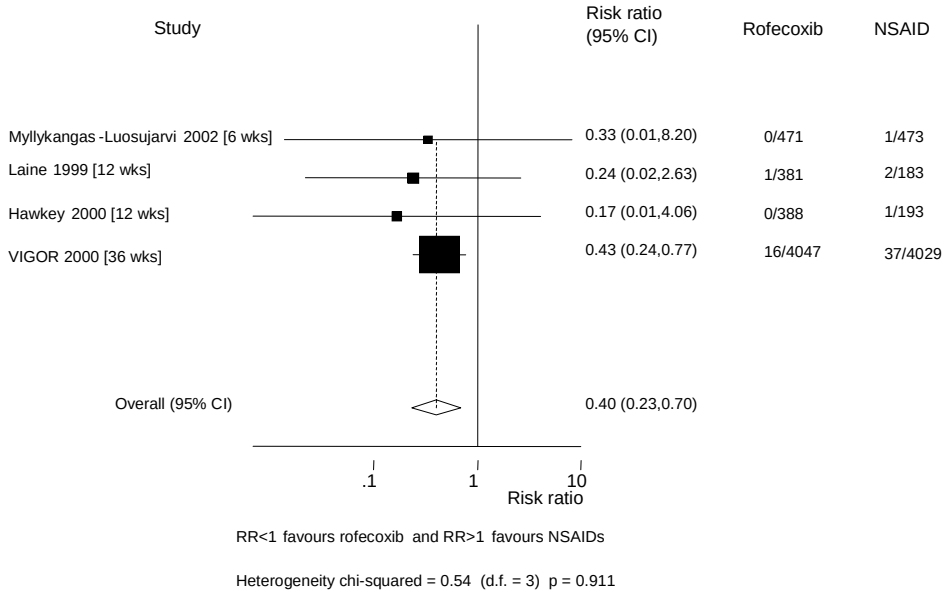


Figure 8: Risk of PUBs with rofecoxib (all doses) vs NSAIDs (all drugs)

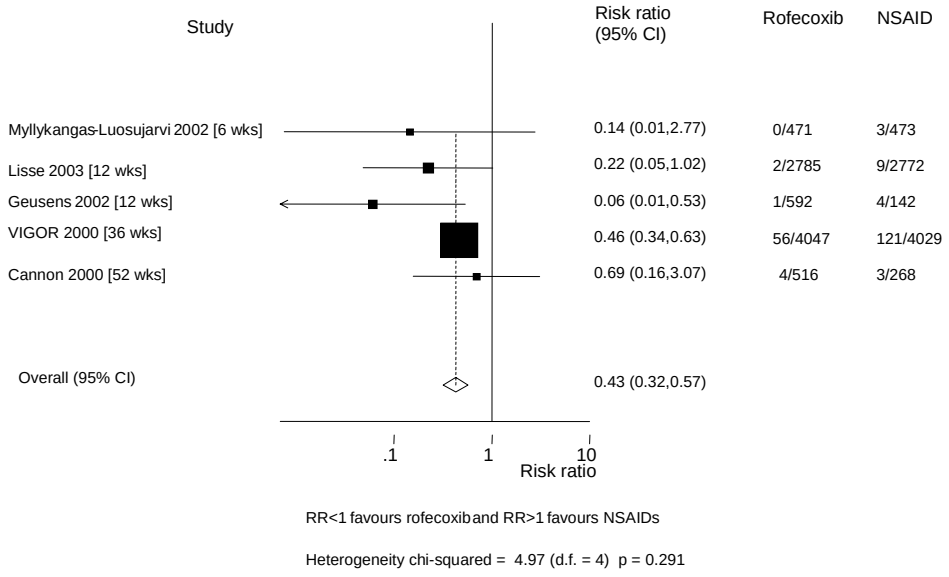
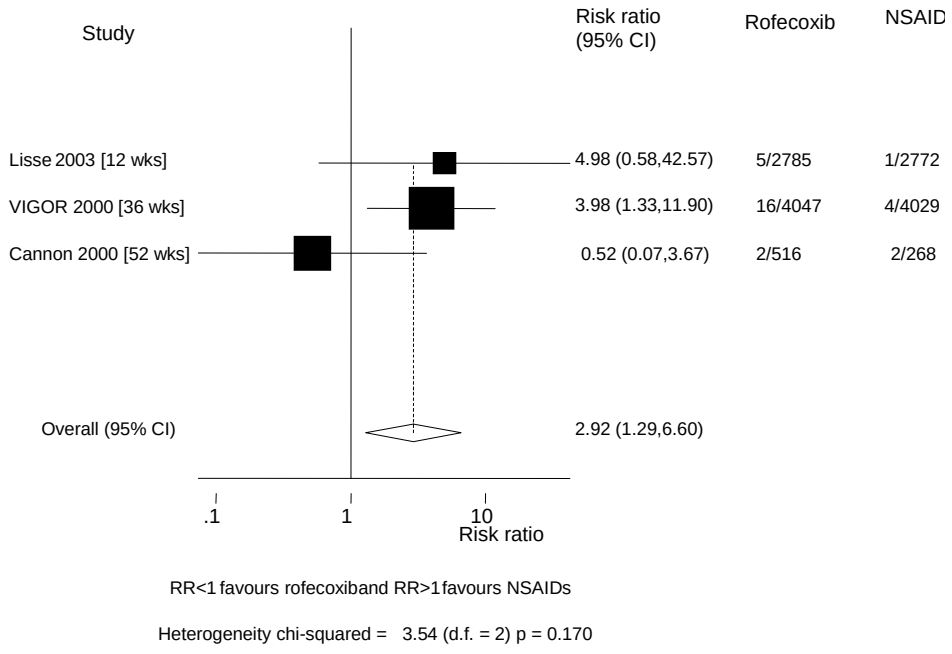


Table 25: Summary of serious cardiovascular thrombotic events for rofecoxib versus placebo or NSAIDs

	Placebo **Relative risk (95% CI)** **[N trials]**	**NSAID** **Relative risk (95% CI)** **[N trials]**
MI		
12.5 mg	Not reported	0.52 (0.05 to 5.67) [1] †
25 mg	¶	2.03 (0.50 to 8.17) [2] †
> 25 mg	¶	*3.98 (1.33 to 11.90) [1]* †
OA only	†	1.75 (0.50 to 6.18) [2] †
RA only	†	*3.98 (1.33 to 11.90) [1]* †
All trials	¶	***2.92 (1.29 to 6.60) [3]*** ¶
Serious CV thrombotic events		
12.5 mg	Not reported	
25 mg	¶	0.50 (0.14 to 1.47) [1] †
> 25 mg	¶	1.02 (0.51 to 2.03) [2] †
OA only	†	*2.36 (1.38 to 4.02) [1]* †
RA only	†	0.89 (0.47 to 1.69) [2] †
All trials	¶	*2.36 (1.38 to 4.02) [1]* **1.31 (0.56 to 3.09) [3] * ¶**

† one trial reported zero events in both arms. ¶ two trials reported zero events in both arms.
*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

Figure 9: Risk of MI with rofecoxib (all doses) vs NSAIDs (all drugs)



4.5.7 Subgroup analysis

Several studies investigated the role of various risk factors on clinical outcomes. These are summarised below.

H pylori status
Data from VIGOR [209] indicated that the benefits of rofecoxib over naproxen were not influenced by evidence of *H.* pylori infection but that the risks of PUBs were significantly greater in *H pylori* positive patients (p=0.04)). However, two endoscopic studies did not find *H. pylori* to be an independent risk factor for gastroduodenal ulcers [192,215], and neither study found a relationship between outcomes of treatment, in terms of toxicity, and *H. pylori* status.

Low-dose aspirin
Withdrawals due to adverse GI events, and use of GI medications, remained lower with rofecoxib than with naproxen regardless of aspirin use [206]. Kivitz and colleagues[207] found that concurrent use of low-dose aspirin did not contribute to an increase in adverse events with rofecoxib or nabumetone.

Age
The benefits of rofecoxib over non-selective agents are maintained regardless of age and studies also confirmed that age over 65 years was a risk factor for gastroduodenal ulcers [192,215]. Drugs were similarly efficacious across different age groups groups.[193,195]

History of prior GI events
Data from VIGOR [209] indicated that the benefits of rofecoxib over naproxen in terms of clinical GI events were similar among patients with (RR = 0.4, 0.2 to 0.8) or without (RR = 0.5, 0.3 to 0.7) prior GI events. Endoscopic studies confirmed that a past history of GI events was was a risk factor of gastroduodenal ulcers [192,215], and the advantage of rofecoxib was maintained in patients with, and those without, prior GI events.[192]

S*teroids and other disease-modifying antirheumatic drugs (DMARDs)*
Patients on steroids in VIGOR appeared to benefit more from rofecoxib in that they had a lesser risk of PUBs, compared with naproxen, than those not on steroids: RR = 0.4 (95% CI 0.2 to 0.6) for steroid users compared with RR = 0.7 (95% CI 0.4 to 1.2) non-users Geusens and colleagues[212] observed no unique efficacy or safety findings or trends in subgroups of patients on low-dose corticosteroids, methotrexate, or other DMARDs.

4.5.8 Impact of concomitant gastroprotective agents

One study, by Acevedo and colleagues, was the only trial included in this review that compared a COX-2 selective NSAID with a non-selective NSAID combined with misoprostol.[216] In this double-blind, multicentre RCT rofecoxib 12.5 mg once daily was compared with Arthrotec (diclofenac 50mg plus misoprostol 0.2 mg) twice daily in 483 OA patients for six weeks. The primary end-point in this trial was self-reported diarrhea. The quality of the trial was judged to be high (Jadad score 5). Unsurprisingly, far more patients on Arthrotec developed diarrhea (16.2%) and other GI symptoms compared with rofecoxib (6.2% diarrhea; p<0.001); since both misoprostol and diclofenac have a propensity to cause diarrhea and abdominal cramping. This trial was not powered to study peptic ulcers or ulcer complications.

4.5.9 Summary

Based on this systematic review and meta-analyses it is concluded that:

- 25 RCTs were included. Studies compared rofecoxib (12.5 to 50mg/day) to either placebo or non-selective NSAIDs (naproxen, etodolac, ibuprofen, arthrotec, combined diclofenac and misoprostol, or nabumetone).
- Rofecoxib is of similar efficacy to non-selective NSAIDs in the symptomatic treatment of OA and RA.
- Rofecoxib was associated with signficiantly lower withdrawals from all adverse events and from GI adverse events compared with non-selective NSAIDs.
- Rofecoxib was associated with significantly fewer endoscopic gastroduodenal ulcers than non-selective NSAIDs and sub-group analyses suggest that the benefit is independent of *H. pylori* infection, age, aspirin use and prior history of GI events, but this conclusion is based on small numbers and needs confirmation.
- Rofecoxib was associated with significantly fewer POBs and PUBs compared with non-selective NSAIDs.
- Myocardial infarctions occurred significantly more commonly in patients treated with rofecoxib than those treated with non-selective NSAIDs.
- Fewer people treated with rofecoxib experience diarrhea, compared with Arthrotec.
- There is no trial evidence comparing etodoloac to non-selective NSAIDs with a GI-procective agent.

4.6 Etodolac

4.6.1 Description of included trials

Twenty-nine trials of etodolac recruiting a total of 5,775 participants met inclusion criteria. Only four trials had placebo controls; various non-selective NSAIDs were used as comparators (naproxen 10, piroxicam 7, diclofenac 4, indomethacin 2, tenoxicam 2, ibuprofen 1, nabumetone 1, nimesulide 1). Full details of the twenty-nine trials are outlined in Appendix 5, pg 210, and summarised in, pg 82. Sample sizes of trials ranged from 20 to 1,446 (median 120) patients. Nineteen of the trials had a sample of less than 200 patients. All but one trial had duration of treatment equal to or less than three months. The only long-term trial, which compared etodolac 300 mg or 1000 mg per day with ibuprofen 2400 mg per day in RA patients, lasted 3 years.

4.6.2 Patient characteristics

Twenty-four trials recruited exclusively OA patients and five trials RA patients. Mean age of patients was between 48 to 71 years. Many of the studies excluded patients with a history of peptic ulcers. Majority (22 out of 27) of the trials were published more than a decade ago (prior 1995) and thus information in relation to *H. pylori* and low-dose aspirin was scant.

4.6.3 Assessment of the quality of included trials

Only two trials were judged to be of good quality (Jadad score 5). Seven trials score only 2 on Jadad scale due to poor reporting of trial methodology. The quality of included trials was summarised in Appendix 6, pg 254.

Table 26: Characteristics and quality of included etodolac randomised controlled trials

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Etodolac	Placebo	NSAID	Efficacy+	Safety+		
Bacon 1990a [217,218]	OA (knee)	600mg per day (300mg bd) (n=70)	-	Naproxen 1000mg per day (500mg bd) (n=73)	Pain (e.g. VAS), Patient's global assessment	-		
Bacon 1990b [217,218]	OA (knee)	600mg per day (300mg bd) (n=170)	-	Piroxicam 20mg per day (20mg od) (n=165)	Pain (e.g. VAS), Patient's global assessment	-		
Bacon 1990c [217,218]	OA (knee)	600mg per day (200mg tds) (n=98)	-	Diclofenac 150mg per day (50mg tds) (n=106)	Pain (e.g. VAS), Patient's global assessment	-		
Williams 1989 [219]	OA (knee, hip)	Knee 600mg per day (300mg bd) (n=50) Hip 600mg per day (300mg bd) (n=54)	Knee n=54 Hip n=52	-	Patient's global assessment	Withdraw events, T Dyspepsi Withdraw		
Freitas 1990 [220]	OA (knee)	600mg per day (300mg bd) (n=33)	-	Piroxicam 20mg per day (20mg od) (n=32)	Patient's global assessment	Withdraw events, T Total car thrombot due to AI		
Brasseur 1991 [221]	OA (knee)	600mg per day (300mg bd) (n=32)	-	Diclofenac SR 100mg per day (100mg od) (n=29)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Dyspepsi Withdraw		
Karbowski 1991 [222]	OA (knee)	600mg per day (300mg bd) (n=31)	-	Indomethacin 150mg per day (50mg tds) (n=33)	Pain (e.g. VAS), Patient's global assessment 'improvement', Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (cli symptom Total PU Dyspepsi		
Palferman 1991 [223]	OA (knee)	600mg per day (300mg bd) (n=29)	-	Naproxen 1000mg per day (500mg bd) (n=27)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Dyspepsi (drug-rel Withdraw		
Paulsen 1991 [224]	OA (knee)	600mg per day (300mg bd) (n=112)	-	Piroxicam 20mg per day	Pain (e.g. VAS), Patient's global assessment,	Withdraw events, T		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Etodolac	Placebo	NSAID	Efficacy+	Safety+		
				(20mg od) (n=108)	Withdrawal due to lack of efficacy	Total PU obstructio Total car thrombot (drug-rel		
Pena 1991 [225]	OA (knee)	600mg per day (300mg bd) (n=31)	-	Naproxen 1000mg per day (500mg bd) (n=31)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Total AE		
Perpignano 1991 [226]	OA (knee, hip)	600mg per day (600mg od) (n=10)	-	Naproxen 750mg per day (750mg od) (n=10)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (en Ulcer (cli symptom Total PU Total AE to GI AE		
Dick 1992 [227]	OA (knee)	600mg per day (300mg bd) (n=57)	-	Piroxicam 20mg per day (20mg od) (n=59)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Dyspepsi Withdraw		
Grisanti 1992 [228]	OA (knee)	600mg per day (600mg od) (n=85)	-	Diclofenac 150mg per day (150mg od) (n=87)	Pain (e.g. VAS), Patient's global assessment	Withdraw events, T Total AE		
Waterworth 1992 [229]	OA (knee)	600mg per day (300mg bd) (n=28)	-	Piroxicam 20mg per day (20mg od) (n=29)	Pain (e.g. VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Dyspepsi		
Burssens 1993 [230]	OA (knee)	600mg per day (600mg od) (n=37)	-	Tenoxicam 20mg per day (20mg od) (n=36)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Total AE		
Eisenkolb 1993 [231]	OA (knee)	600mg per day (600mg od) (n=66)	-	Diclofenac 150mg per day (150mg od) (n=69)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Total car thrombot severe, T Withdraw		
Chikanza 1994	OA	600mg per day	-	Naproxen	Pain (e.g. VAS), Patient's	Withdraw		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Etodolac	Placebo	NSAID	Efficacy+	Safety+		
[232]	(knee, hip)	(300mg bd) (n=39) for 4 wks		1000mg per day (500mg bd) (n=37) for 4 wks	global assessment, Withdrawal due to lack of efficacy	events, T Total AE		
Lucker 1994 [233]	OA (knee)	600mg per day (600mg od) (n=99)	-	Nimesulide 200mg per day (200mg od) (n=100)	Pain (e.g. VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Total AE		
Perpignano 1994 [234]	OA (knee, hip)	600mg per day (600mg od) (n=60)	-	Tenoxicam 20mg per day (20mg od) (n=60)	Pain (e.g. VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Total AE		
Dore 1995 [235]	OA (knee)	800mg per day (400mg bd) (n=86)	n=86	Naproxen 1000mg per day (500mg bd) (n=82)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Total PU obstructi Total AE Withdraw		
Schnitzer 1995 [236]	OA (knee)	800mg per day (400mg bd) (n=91)	n=90	Nabumetone 1500mg per day (1500mg od) (n=89)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Dyspepsi ('treatme		
Jennings 1997 [237]	OA (foot, ankle)	800mg per day (400mg bd) (n=29)	-	Naproxen 1000mg per day (500mg bd) (n=31)	-	Withdraw events, T		
Rogind 1997 [238]	OA (knee, hip)	600mg per day (300mg bd) (n=138)	-	Piroxicam 40mg per day (20mg bd) (n=133)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (cli symptom cardiovas Total AE		
Schnitzer 1997 [239]	OA (knee)	400mg qd 200mg qd (n=424) (total number of patients on all drugs)	n=424 (total number of patients on all drugs)	Naproxen 1000mg per day (500mg bd) (n=424) (total number of patients on all drugs)	Patient's global assessment, Withdrawal due to lack of efficacy	Total wit PUB, Tot		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Etodolac	Placebo	NSAID	Efficacy+	Safety+		
Taha 1989 [240,241]	RA	600mg per day (300mg bd) (n=50)	-	Naproxen 1000mg per day (500mg bd) (n=57)	Pain (e.g. VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (en given; fra Ulcer (cli symptom Total PU		
Delcambre 1990 [207]	RA	600mg per day (200mg tds) (n=50)	-	Indomethacin 100mg per day (25mg bd and 50mg od) (n=52)	Spontaneous global pain (VAS, 100 mm scale), Patient's global assessment (on efficacy), Patients global assessment (on tolerance), Withdrawal due to lack of efficacy	Withdraw events, T Total AE		
Taha 1990 [241,242]	RA	600mg per day (300mg bd) (n=14)	-	Naproxen 1000mg per day (500mg bd) (n=13)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (en given; fra Ulcer (cli symptom Total PU		
Lightfoot 1997 [243]	RA	400mg per day (200mg bd) (n=140) 600mg per day (300mg bd) (n=147)	-	Piroxicam 80mg per day (20mg qds) (n=139)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (cli symptom		
Neustadt 1997 [244]	RA	300mg per day (150mg bd) (n=620) 1000mg per day (500mg bd) (n=409)	-	Ibuprofen 600mg qd (n=417)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (cli symptom		

4.6.4 Assessment of etodolac efficacy

The efficacy results across trials are summarised in Table 27, pg 88. It was not possible to carry out meta-analyses for several efficacy outcomes because of the variations in the assessment methods used and poor reporting of the variance of outcome measures.

Patient's assessment of arthritis pain
Etodolac was equivalent to non-selective NSAIDs for pain relief in OA patients. One RA trial observed no significant difference between etodolac 600 mg per day and indomethacin 100 mg per day.

Patient's assessment of global efficacy
Etodolac was equally efficacious compared with non-selective NSAIDs.

ACR-20 responder
No trial reported ACR-20 outcome.

Withdrawals due to lack of efficacy
Etodolac was associated with similar levels of withdrawals due to lack of efficacy compared to non-selective NSAIDs.

Table 27: Summary of efficacy results of etodolac versus placebo and NSAIDs

	Placebo				NS			
	Pain	**Global efficacy difference Mean (95% CI)**	**ACR-20 RR (95% CI)**	**Withdrawals due to lack of efficacy RR (95% CI)**	**Pain difference Mean (95% CI)**	**Global efficacy difference Mean (95% CI)**		
600 mg	[1]$	[1]$	No trials	No trials	2.06 (-2.09 to 6.22) [2]	-0.08 (-0.25 t 0.09) [3] ‡		
>600 mg	[3] $	[3] $	No trials	*0.29 (0.18 to 0.45)* [3]	[4] $	No differenc or etodolac better [4] $		
OA only	[4] $	[4] $	No trials	*0.29 (0.18 to 0.45)* [3]	2.06 (-2.09 to 6.22) [2]	-0.00 (0.22 to 0.22) [2] ‡		
RA only	No trials	No trials	No trials	No trial	[1] $	-0.20 (-0.46 t 0.06) [1]		
All trials	[4] $	[4] $	No trials	***0.29 (0.18 to 0.45)* [3]**	**2.06 (-2.09 to 6.22) [2]**	**-0.08 (-0.25 t 0.09) [3] ‡**		

* Heterogeneity P<0.01 & random effects model used
$Insufficient data for meta-analysis; [ ]: N trials

4.6.5 Etodolac tolerability

Adverse events

Compared with non-selective NSAIDs, etodolac was associated with lower risk of all adverse events and GI adverse events.

Withdrawals

There was no difference between etodolac and non-selective NSAIDs for withdrawals due to adverse events, GI adverse events and for all causes.

Table 28: Summary of adverse events for etodolac versus placebo & NSAIDs

	Placebo **Relative risk (95% CI) [N trials]**	**NSAIDs** **Relative risk (95% CI) [N trials]**
All adverse events		
600mg	1.47 (0.86 to 2.52) [1]	*0.76 (0.60 to 0.95) [9]* *
>600 mg	1.38 (0.95 to 2.00) [2] *	1.00 (0.86 to 1.17) [3]
OA only	*1.43 (1.19 to 1.73) [3]*	0.85 (0.71 to 1.01) [11] *
RA only	Not reported	0.62 (0.34 to 1.14) [1]
All trials	***1.43 (1.19 to 1.73) [3]***	***0.83 (0.70 to 0.99) [12] ****
GI adverse events		
600mg	1.53 (0.78 to 3.01) [1]	*0.68 (0.53 to 0.87) [8]*
>600 mg	*1.93 (1.12 to 3.34) [1]*	1.38 (0.85 to 2.24) [1]
OA only	*1.75 (1.15 to 2.68) [2]*	0.77 (0.55 to 1.08) [9] *
RA only	Not reported	not reported
All trials	***1.75 (1.15 to 2.68) [2]***	**0.77 (0.55 to 1.08) [9] ***

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

Table 29: Summary of withdrawals for etodolac versus placebo & NSAIDs

	Placebo **Relative risk (95% CI) [N trials]**	**NSAIDs** **Relative risk (95% CI) [N trials]**
All adverse event withdrawals		
600mg	1.22 (0.39 to 3.88) [1]	0.89 (0.69 to1.16) [17]
>600 mg	0.89 (0.54 to 1.48) [3]	0.96 (0.74 to 1.25) [5]
OA only	0.94 (0.59 to 1.49) [4]	0.94 (0.74 to 1.20) [19]
RA only	Not reported	0.90 (0.68 to 1.20) [3]
All trials	**0.94 (0.59 to 1.49) [4]**	**0.93 (0.77 to 1.12) [22]**
All GI withdrawals		
600mg	1.02 (0.26 to 3.97) [1]	0.99 (0.56 to 1.75) [7]
>600 mg	0.33 (0.01 to 8.07) [1]	0.32 (0.01 to 7.70) [1]
OA only	0.83 (0.24 to 2.83) [2]	0.95 (0.54 to 1.65) [8]
RA only	Not reported	Not reported
All trials	**0.83 (0.24 to 2.83) [2]**	**0.95 (0.54 to 1.65) [8]**
All withdrawals		
600mg	Not reported	0.96 (0.80 to 1.14) [17]
>600 mg	*0.50 (0.39 to 0.65) [3]*	0.98 (0.91 to 1.06) [4]
OA only	*0.50 (0.39 to 0.65) [3]*	1.01 (0.84 to 1.20) [18]
RA only	Not reported	0.96 (0.89 to 1.03) [3]
All trials	***0.50 (0.39 to 0.65) [3]***	**0.97 (0.90 to 1.05) [21]**

4.6.6 Safety of etodolac

Endoscopic ulcers
One trial reported no difference in endoscopic ulcers between etodolac and non-selective NSAIDs.

Clinical UGI events (PUBs) and complicated UGI events (POBs)
Based on predominantly short- term trials, etodolac appears to be associated with fewer PUBs (RR: 0.32, 0.15-0.71; NNT: 74, 59-174) and a similar level of POBs compared with non-selective NSAIDs.

Myocardial infarctions and all thrombotic events
No trials reported the risk of MI. There was no significant difference in all thrombotic events in patients treated with etodolac compared to non-selective NSAIDs.

Table 30: Summary of endoscopic GI ulcers and clinical and complicated UGI events (PUBs and POBs) for etodolac versus placebo or NSAIDs

	Placebo Relative risk (95% CI) [N trials]	**NSAID Relative risk (95% CI) [N trials]**
Endoscopic GI ulcers		
600mg	Not reported	0.50 (0.05 to 4.67) [1] †
>600 mg		Not reported
OA only		0.50 (0.05 to 4.67) [1] †
RA only		†
All trials		**0.50 (0.05 to 4.67) [1]** †
POBs		
600mg	†	0.41 (0.12 to 1.40) [5] ¶
>600 mg	1.14 (0.86 to 1.52) [1]	0.32 (0.01 to 7.70) [1]
OA only	1.14 (0.86 to 1.52) [1] †	0.46 (0.13 to 1.63) [6] †
RA only	Not reported	0.19 (0.01 to 3.91) [1] †
All trials	**1.14 (0.86 to 1.52) [1]** †	**0.39 (0.12 to 1.24) [6]** ¶
PUBs		
600mg	†	0.39 (0.13 to 1.14) [6]
>600 mg	0.69 (0.08 to 5.67) [2]	0.32 (0.10 to 1.05) [3]
OA only	0.69 (0.08 to 5.67) [2] †	0.45 (0.17 to 1.22) [7]
RA only	Not reported	*0.20 (0.05 to 0.77) [2]*
All trials	**0.69 (0.08 to 5.67) [2]** †	***0.32 (0.15 to 0.71) [9]*** †

† one trial reported zero events in both arms. ¶ two trials reported zero events in both arms.

Figure 10: Risk of POBs with etodolac (all doses) vs NSAIDs (all drugs)

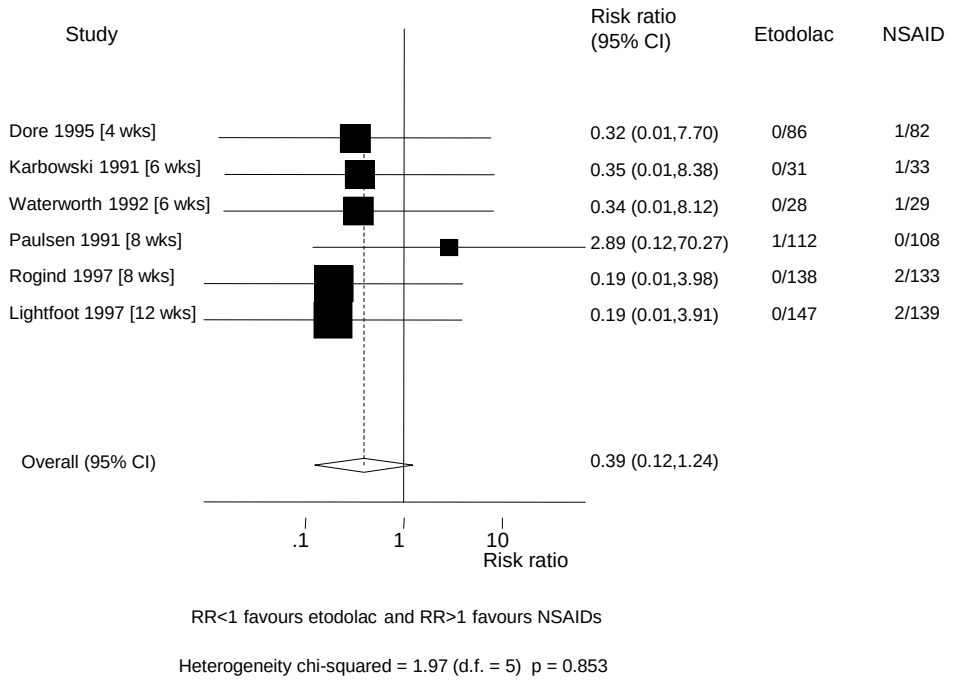


Figure 11: Risk of PUBs with etodolac (all doses) vs NSAIDs (all drugs)

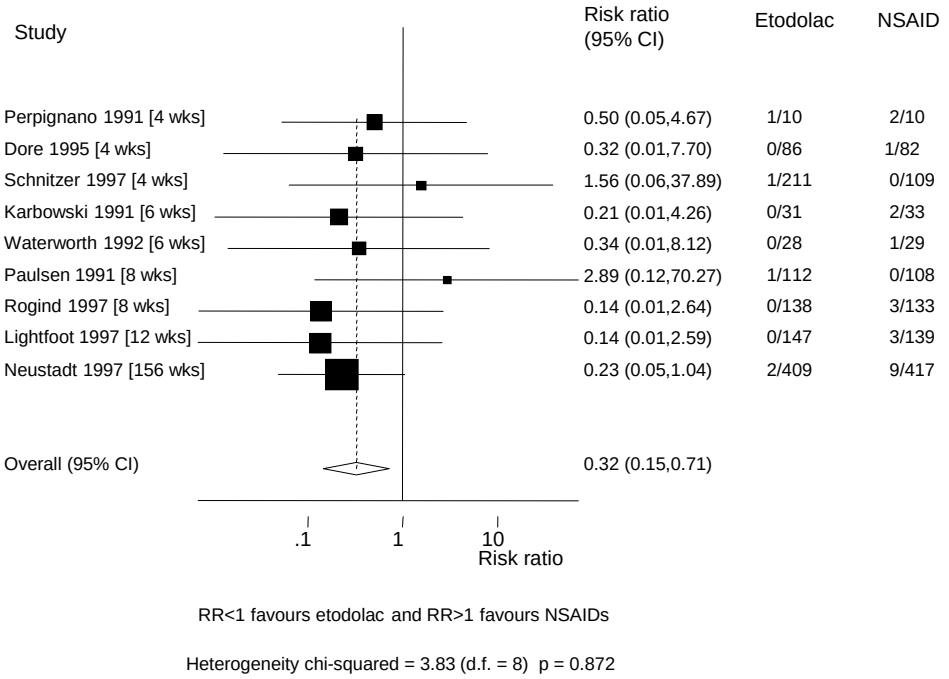


Table 31: Summary of serious cardiovascular thrombotic events for etodolac versus placebo or NSAIDs

	Placebo **Relative risk (95% CI) [N trials]**	**NSAID** **Relative risk (95% CI) [N trials]**
MI	Not reported	Not reported
Serious CV thrombotic events 600mg >600 mg OA only RA only **All trials**	Not reported	 0.50 (0.09 to 2.66) [2] Not reported 0.50 (0.09 to 2.66) [2] Not reported **0.50 (0.09 to 2.66) [2]**

† one trial reported zero events in both arms. ¶ two trials reported zero events in both arms.

4.6.7 Subgroup analyses

Few trials reported the results of subgroup analysis. Williams and colleague[219] reported slightly higher risk of adverse events in patients older than 65 years in both etodolac and placebo groups.

4.6.8 Impact of concomitant gastroprotective agents

No trials addressing this issue were identified.

4.6.9 Summary

Based on the systematic review and meta-analyses, it is concluded that:

- 29 RCTs were included. Studies compared etodolac (600 to 800 mg/day) to either placebo or non- selective NSAIDs (naproxen, piroxicam, diclofenac, indomethacin, tenoxicam, ibuprofen, nabumetone and or nimesulide).
- Etodolac is of equivalent efficacy to non-selective NSAIDs.
- Etodolac was associated with a lower risk of all adverse events compared to non-selective NSAIDs.
- Withdrawals due to adverse events, GI adverse events and for all cases were equivalent between etodolac and non-selective NSAIDs .
- Etodolac appears to be associated with fewer PUBs and POBs than non-selective NSAID but this conclusion is based on very few events and requires confirmation.
- There is no trial evidence to assess the effects of etodolac on myocardial infaection.
- There is insufficient trial evidence to comment on the GI safety of etodolac in high risk patients, those taking low dose aspirin or antigoagulants, or according to *H Pylori* status.
- There is no trial evidence comparing etodoloac to non-selective NSAIDs with a GI-procective agent.

4.7 Etoricoxib

4.7.1 Description of included trials

Seven trials of etoricoxib met inclusion criteria. Full details of these trials are outlined in Appendix 5, pg 210 and summarised in Table 32, pg 95.
Trials were relatively small and no trial recruited over 1,000 patients. Trials ranged from 6-weeks to 14-months.

Patient characteristics
Four trials recruited only OA, two trials RA patients and two trials both OA and RA. The mean age of trial patients ranged from 52 to 63 years, 66% to 82 % were female and of functional class I to III (the most severely disabled people, class IV, were excluded, in common with most NSAID trials). Patient characteristics were relatively well reported: 8% to 10% of participants had experienced a previous GI ulcer; 0% to 7% were taking low dose aspirin; 32% to 59% oral corticosteroids; and 57% to 60% were *H. Pylori* positive. Virtually all included patients were already taking NSAIDs at the time of recruitment.

Study interventions
Etoricoxib at licensed doses (60mg and 90mg per day) was studied in five trials and two trials included supra-license doses (120 mg per day). Six trials compared etoricoxib to placebo and all compared etoricoxib to non-selective NSAIDs: diclofenac (2/7); naproxen (4/13); and. ibuprofen (1/13).

4.7.2 Assessment of the quality of included trials

The median Jadad score across trials was 4 indicating the trials were generally of 'moderate' to 'good' quality (see Table 32 pg 95). A full summary of the quality of trials is provided in Appendix 6, pg 254.

The three trials that scored poorly (Jadad score of 3) did so because of poor reporting of trial methods. Four trials provided adequate details of randomisation and concealment, six were double blind and four described intention to treat analysis. Loss to follow-up, where reported ranged from <5% to 17%. As with other COX-2 selective drugs, a large proportion of withdrawals and a higher level in the non-selective NSAID arm of trials led to the potential of bias in favour of non-selective NSAIDs.

Table 32: Characteristics and quality of included etoricoxib randomised controlled trials

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Etoricoxib	Placebo	NSAID	Efficacy+	Safety+		
Gottesdiener 2002, MSD Study 007[245,246]	OA (knee)	5mg per day (5 mg od) (n=117) 10mg per day (10 mg od) (n=114) 30mg per day (30 mg od) (n=102) 60mg per day (60 mg od) (n=112) 90mg per day (90 mg od) (n=112)	n=60	-	Pain (WOMAC), patient global assessment (response to therapy), Withdrawal due to lack of efficacy	Withdrawal events, Tot Ulcer (endo Ulcer (clini symptomati Total PUB Dyspepsia, infarction, cardiovascu Total AE se		
Leung 2002, MSD Study 019[247]	OA (knee or hip)	60mg per day (60 mg od) (n=224)	n=56	Naproxen 1000mg per day (500 mg bd) (n=221)	WOMAC pain, WOMAC physical function subscale, WOMAC stiffness, Withdrawal due to lack of efficacy	Withdrawal events, Tot Ulcer (clini symptomati Dyspepsia, infarction, cardiovascu Total AE se Withdrawal		
Hunt 2003a, MSD Study 029[248]	OA (site not stated)	120mg per day (120 mg od) (n=221)	n=233	Ibuprofen 2400mg per day (800 mg tds) (n=226)	Withdrawal due to lack of efficacy	Withdrawal events, Tot Ulcer (endo and/ or duo severe, Tot Withdrawal		
Zacher 2003, MSD Study 805[249]	OA (knee or hip)	60mg per day (60 mg od) (n=256)	-	Diclofenac 150mg per day (50 mg tds) (n=260)	Pain (VAS), Functional status (WOMAC), Patient's global assessment	Withdrawal events, Wit drug relatec Total withd severe, Tot		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Etoricoxib	Placebo	NSAID	Efficacy+	Safety+		
Collantes 2002, MSD Study 025[250]	RA	90mg per day (90 mg od) (n=353)	n=357	Naproxen 1000mg per day (500 mg bd) (n=181)	Pain – patient global (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdrawal events, Tota Ulcer (clini symptomati Total PUB Myocardial cardiovascu Total AE sc Withdrawal		
Matsumoto 2002, MSD Study 024[251]	RA	90mg per day (90 mg od) (n=323)	n=323	Naproxen 1000mg per day (500 mg bd) (n=170)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdrawal events, Tota Total PUB, obstruction, Myocardial cardiovascu Total AE sc Withdrawal		
Hunt 2003b, MSD Study 026[252]	OA (site not stated) or RA	120mg per day (120 mg od) (n=251)	n=247	Naproxen 1000mg per day (500 mg bd) (n=244)	Withdrawal due to lack of efficacy	Withdrawal events, Tota Ulcer (endo >3MM), To related), W GI AE		

4.7.3 Assessment of etoricoxib efficacy

The efficacy results across trials are summarised in Table 33, pg 99.

Patient's assessment of arthritis pain
In comparison to non-selective NSAIDs, etoricoxib was equivalent in pain relief. These results appeared relatively consistent across etoricoxib doses and with both OA and RA patients.

Patient's assessment of global efficacy
Global efficacy for etoricoxib was equivalent to non-selective NSAIDs. These results appeared to be consistent across etoricoxib doses and with both OA and RA patients.

ACR-20 responder
ACR-20 was equivalent for etroricoxib to conventional NSAIDs.

Withdrawals due to lack of efficacy
A similar number of patients on etoricoxib withdrew due to lack of efficacy compared with non-selective NSAIDs. These results, again, appeared to be consistent to both OA and RA patients and across etoricoxib doses.

Table 33: Summary of efficacy results of etoricoxib versus placebo and NSAIDS

	Placebo				NS			
	VAS pain difference mean (95% CI)	**Global efficacy (VAS) difference**	**ACR-20 RR (95% CI)**	**Withdrawals due to lack of efficacy**	**VAS pain difference mean (95% CI)**	**Global efficacy (VAS) difference**		
60 mg	*-15.81(-26.66 to -4.97) [2] **	*-9.34 (-15.72 to -2.96) [1]*	No trials	*0.33 (0.14 to 0.76) [2]*	-0.42 (-3.65 to 2.85) [2]	-1.75 (-5.91 to 2.41) [1]		
90 mg	*-16.29 (-19.28 to -13.30)* [2]	*-13.25 (-21.78 to -4.73) [2] **	*1.73 (1.18 to 2.52) [2] **	*0.50 (0.41 to 0.60) [3]*	*-6.7 (-10.6 to -2.8) [1]*	-2.61 (-10.06 to 4.83) [2] *		
>90mg	No trials	No trials	No trials	*0.40 (0.18 to 0.90) [2]*	No trials	No trials		
OA only	*-15.24 (-24.86 to -5.62) [2] **	*-9.34 (-15.72 to –2.96) [1]*	No trials	*0.25 (0.12 to 0.50) [3]*	-0.42 (-2.94 to 2.10) [2]	-1.75 (-5.91 to 2.41) [1]		
RA only	*-15.8 (-19.1 to -12.6) [1]*	*-13.25 (-21.78 to -4.73*) [2] *	1.22 (0.87 to 1.70) [2] *	*0.43 (0.36 to 0.52) [2]*	*-6.7 (-10.6 to -2.8) [1]*	-2.61 (-10.06 to 4.83) [2] *		
All trials	***-15.48 (-20.50 to -10.46) [3] ****	***-12.10 (-18.05 to -6.15) [3] ****	**1.22 (0.87 to 1.70) [2] ***	***0.42 (0.35 to 0.50) [6]***	**-2.50 (-6.55 to 1.56) [3] ***	**-2.24 (-6.36 to 1.88) [3] ***		

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

4.7.4 Etoricoxib tolerability

Adverse events

There was no significant difference in overall adverse events for etoricoxib compared to placebo or non-selective NSAID. Specific data on GI adverse events were not reported (see Table 34, pg 101).

Withdrawals

Etoricoxib significantly reduced the level of both overall and GI-specific withdrawals compared to non-selective NSAIDs (see Table 34, pg 101).

4.7.5 Safety of etoricoxib

Outcomes such as PUBs, POBs, MIs and thromboemobolitic events were reported in three trials (see Table 34, pg 101).

Endoscopic GI ulcers

Endoscopic ulcers were assessed in two 12-week studies.[248,252] Both studies used etoricoxib 120 mg daily (supra-license dose), one included OA patients and another included both OA and RA patients. Cumulative incidences of ulcers were calculated using survival analysis methods, taking into account of patient withdrawals. Results showed etoricoxib was associated with significantly fewer endoscopic gastroduodenal ulcers compared with non-selective NSAIDs.[253]

Clinical and complicated UGI events (PUBs & POBs)

There was no significant difference in PUBs and POBs compared to non-selective NSAIDs.

Myocardial infarctions and thromboemobolic events

Only one trial, with few MIs and thromboemolic events, was identified. There was no evidence of a significant difference between etoricoxib and non-selective NSAIDs.

Table 34: Summary of tolerability and safety outcomes for etoricoxib versus placebo and NSAIDS

	Placebo Relative Risk (95% CI) [N trials]	**NSAIDs Relative Risk (95% CI) [N trials]**
All adverse events		
60mg	not reported	not reported
90 mg	not reported	not reported
120 mg	1.05 (0.89 to 1.25) [1]	0.98 (0.83 to 1.15) [1]
OA only	1.05 (0.89 to 1.25) [1]	0.98 (0.83 to 1.15) [1]
RA only	not reported	not reported
All trials	**1.05 (0.89 to 1.25) [1]**	**0.98 (0.83 to 1.15) [1]**
GI adverse events	No trials*	No trials*

*: specific GI AEs reported but not overall GI AEs

Table 35: Summary of tolerability and safety outcomes for etoricoxib versus placebo and NSAIDs

	Placebo Relative Risk (95% CI) [N trials]	**NSAIDs Relative Risk (95% CI) [N trials]**
All adverse event withdrawals		
60mg	*0.34 (0.13 to 0.84)* [2]	0.58 (0.08 to 4.34) [2]*
90 mg	1.03 (0.59 to 1.80) [3]	0.80 (0.40 to 1.59) [2]
120 mg	1.43 (0.87 to 2.34) [2]	0.87 (0.56 to 1.34) [2]
OA only	0.79 (0.19 to 3.23) [3]*	0.78 (0.24 to 2.48) [3]*
RA only	0.96 (0.52 to 1.75) [2]	0.80 (0.40 to 1.59) [2]
All trials	**0.95 (0.56 to 1.60) [7] ***	**0.67 (0.39 to 1.15) [6]***
All GI withdrawals		
60mg	0.75 (0.08 to 7.07) [1]	*0.20 (0.06 to 0.67)* [1]
90 mg	0.84 (0.26 to 2.72) [2]	0.43 (0.13 to 1.41) [2]
120 mg	*9.84 (1.27 to 76.3)* [1]	*0.44 (0.21 to 0.91)* [1]
OA only	0.75 (0.08 to 7.07) [1]	*0.20 (0.06 to 0.67)* [1]
RA only	0.96 (0.52 to 1.75) [2]	0.38 (0.12 to 1.24) [2]
All trials	**1.88 (0.83 to 4.27) [4]**	***0.36 (0.21 to 0.62)* [4]**
All withdrawals		
60mg	*0.44 (0.26 to 0.74)* [2]	*0.53 (0.32 to 0.89)* [1]
90 mg	*0.49 (0.42 to 0.57)* [3]	0.79 (0.52 to 1.20) [2]
120 mg	0.82 (0.60 to 1.11) [2]	0.89 (0.54 to 1.45) [1]
OA only	*0.61 (0.44 to 0.85)* [3]	0.79 (0.52 to 1.20) [2]
RA only	*0.49 (0.41 to 0.57)* [2]	*0.69 (0.49 to 0.98)* [2]
All trials	***0.57 (0.45 to 0.71)* [6] ***	***0.76 (0.64 to 0.90)* [5]***

*: significant (P≤0.01) heterogeneity – random effects meta-analysis

Table 36: Summary of endoscopic GI ulcers and clinical and complicated UGI events (PUBs and POBs) for etoricoxib versus placebo and NSAIDs

	Placebo Relative Risk (95% CI) [N trials]	**NSAIDs Relative Risk (95% CI) [N trials]**
Endoscopic ulcer		
60mg	No trials	No trials
90 mg	No trials	No trials
120 mg	[2] $	[2] $
OA only	[1] $	[1] $
RA only	No trials	No trial
All trials	[2] $	[2] $
POBs		
60mg	¶	not reported
90 mg	‡	0.18 (0.01 to 4.29) [1] †
120 mg	3.16 (0.13 to 77.2) [1]	1.02 (0.06 to 16.2) [1]
OA only	1.71 (0.20 to 14.6) [2]†	1.02 (0.06 to 16.2) [1]
RA only	¶	0.18 (0.01 to 4.30) [1] †
All trials	**1.71 (0.20 to 14.6) [2]‡**	**0.46 (0.07 to 3.10) [2] †**
PUBs		
60mg	¶	0.09 (0.00 to 1.61) [1]
90 mg	3.03 (0.12 to 74.2) [1] ¶	0.52 (0.07 to 3.70) [2]
120 mg	not reported	not reported
OA only	0.81 (0.03 to 19.7) [1] †	0.09 (0.01 to 1.61) [1]
RA only	3.03 (0.12 to 74.2) [1] †	0.52 (0.07 to 3.70) [2]
All trials	**1.67 (0.19 to 14.4) [2]¶**	**0.23 (0.05 to 1.08) [3]**

$ Meta-analysis not carried out as it was not possible to calculate RR or hazard ratio from survival analysis data reported by trials. † one trial reported zero events in both arms.
¶ two trials reported zero events in both arms. ‡ three trials reported zero events in both arms.

Table 37: Summary of endoscopic GI ulcers and clinical and complicated UGI events (PUBs and POBs) for etoricoxib versus placebo and NSAIDs

	Placebo Relative Risk (95% CI) [N trials]	NSAIDs Relative Risk (95% CI) [N trials]
MI		
60mg	¶	†
90 mg	3.0 (0.12 to 73.4) [1] ¶	1.58 (0.06 to 38.66) [1] †
120 mg	not reported	not reported
OA only	¶	†
RA only	3.0 (0.12 to 73.4) [1] †	1.58 (0.06 to 38.66) [1] †
All trials	**3.0 (0.12 to 73.4) [1] ‡**	**1.58 (0.06 to 38.66) [1] ¶**
Serious CV thrombotic events		
60mg	¶	†
90 mg	3.0 (0.12 to 73.4) [1] ¶	1.58 (0.06 to 38.66) [1] †
120 mg	not reported	not reported
OA only	¶	†
RA only	3.0 (0.12 to 73.4) [1] †	1.58 (0.06 to 38.66) [1] †
All trials	**3.0 (0.12 to 73.4) [1] ‡**	**1.58 (0.06 to 38.66) [1] ¶**

† one trial reported zero events in both arms. ¶ two trials reported zero events in both arms.
‡ three trials reported zero events in both arms.

Figure 12: Risk of POBs with etoricoxib (all doses) vs NSAIDs (all drugs)

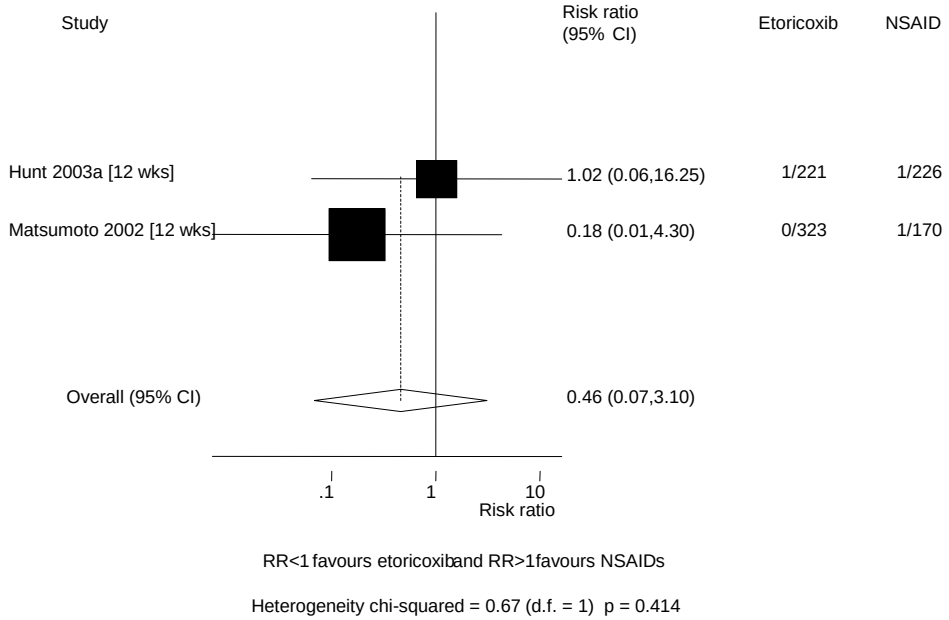
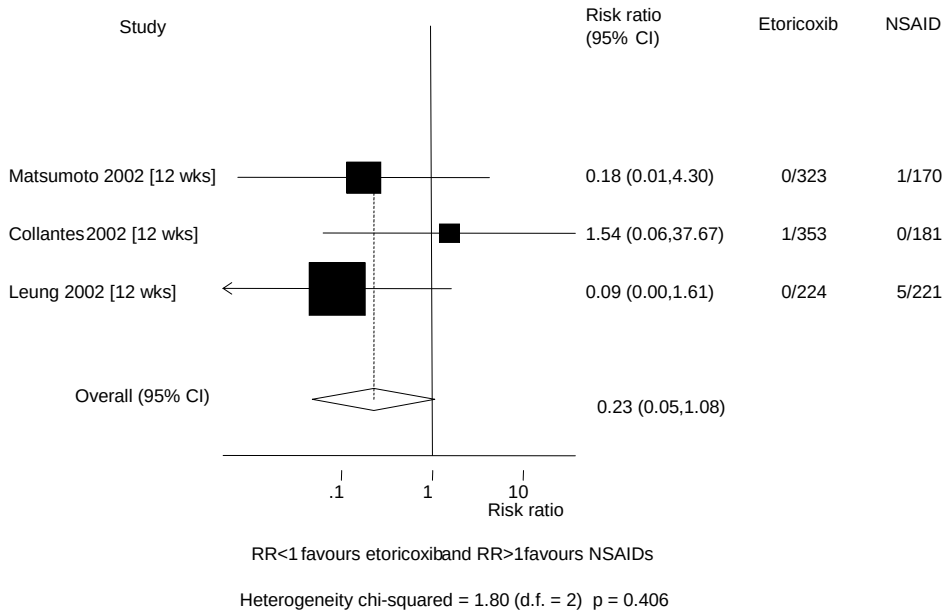


Figure 13: Risk of PUBs with etoricoxib (all doses) vs NSAIDs (all drugs)



4.7.6 Subgroup analyses

One trial found that age and functional status did not affect the degree of pain relief obtained with etoricoxib (60mg per day) or diclofenac (50mg three times per day).[249] No subgroup analyses for adverse effects were available.

4.7.7 Impact of concomitant gastroprotective agents

No relevant trials identified.

4.7.8 Summary

Based on the systematic review and meta-analysis, it is concluded that:

- 6 RCTs were included. Studies compared etoricoxib (60 to 120mg/day) to either placebo or non-selective NSAIDs (naproxen, diclofenac and ibuprofen).
- Etoricoxib is of equivalent efficacy to non-selective NSAIDs in the symptomatic treatment of OA and RA.
- Etoricoxib is associated with significantly fewer GI-related withdrawals compared to non-selective NSAIDs.
- Etoricoxib is associated with significantly fewer endoscopic GI ulcers than non-selective NSAIDs.
- Etoricoxib appears to be associated with fewer PUBs and POBs than non-selective NSAID but this conclusion is based on very few events and requires confirmation.
- There is currently insufficient trial evidence to determine whether the incidence of PUBs, POBs, MIs and thromboembolic events is different between etoricoxib and non-selective NSAIDs.

- No trial evidence was found examining the relative benefits of etoricoxib in patients taking low dose aspirin, anticoagulants or with H. pylori infection. Also no trial has compared etoricoxib with non-selective NSAIDs combined with a gastro-protective agent.

4.8 Valdecoxib

4.8.1 Description of included trials

Eleven trials of valdecoxib recruiting a total of 9,293 participants met inclusion criteria, nine trials had placebo controls and ten used one or two non-selective NSAIDs as comparators (naproxen 7, ibuprofen 1, diclofenac 3). One trial compared valdecoxib with rofecoxib and placebo. The direct comparison with rofecoxib is described in section 4.9 while the comparison with placebo is included in this section. Full details of the eleven trials are outlined in appendix 5 and summarised in Table 38, pg 108. Sample sizes of trials ranged from 467 to 1,218 (median 782) patients. Trials lasted from two weeks to six months: a majority (8/11) lasted three months or less.

4.8.2 Patient characteristics

Six trials recruited exclusively OA patients, four trials RA patients and one trial both OA and RA patients. Mean age of patients was between 55 to 64 years. Low-dose aspirin was permitted in most trials but the proportion of patients on aspirin was not well reported.

4.8.3 Assessment of the quality of included trials

Included trials were generally of good quality; eight out of eleven scored 5 on the Jadad scale. A full summary of the quality of the trials is provided in Appendix 6, 254.

Table 38: Characteristic and quality of included valdecoxib randomised controlled trials

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Valdecoxib	Placebo	NSAID	Efficacy+	Safety+		
Fiechtner 2001, Pfizer Study 015	OA (knee)	1mg per day (0.5mg bd) (n=77) 2.5mg per day (1.25mg bd) (n=81) 5mg per day (2.5mg bd) (n=83) 10mg per day (5mg bd) (n=83) 10mg per day (10mg od) (n=82) 20mg per day (10mg bd) (n=79)	n=82	Naproxen 1000mg per day (500mg bd) (n=75)	Patient's assessment of arthritis pain (VAS), Functional status (e.g. WOMAC), WOMAC composite, Patient's global assessment of arthritis, Withdrawal due to lack of efficacy	Total wit PUB, Ulc def:) Gas Dyspepsi infarctior cardiovas Total AE Withdrav Withdrav		
Kivitz 2002, Pfizer Study 053 [254]	OA (knee)	5mg per day (5mg od) (n=201) 10mg per day (10mg od) (n=206) 20mg per day (20mg od) (n=202)	n=205	Naproxen 500mg per day (500mg od) (n=205)	Pain (e.g. VAS), Functional status (e.g. WOMAC), Stiffness, Patient's global assessment, Withdrawal due to lack of efficacy	Withdrav events, T Ulcer (all def: >5m Ulcer: du (clinical dyspepsia		
Makarowski 2002, Pfizer Study 049 [255]	OA (hip)	5mg per day (5mg od) (n=120) 10mg per day (10mg od) (n=111)	n=118	Naproxen 1000mg per day (500mg bd) (n=118)	Pain (e.g. VAS), WOMAC Functional, WOMAC stiffness index, WOMAC composite, Patient global assessment of arthritis, Withdrawal due to lack of efficacy	Withdrav events, T Dyspepsi Withdrav		
Sikes 2002, Pfizer Study 048 [256]	OA (not stated)	10mg per day (10mg od) (n=204) 20mg per day (20mg od) (n=219)	n=210	Diclofenac 150mg per day (75mg bd) (n=212), Ibuprofen 2400mg per day (800mg tds) (n=207)	Patient's global assessment, Withdrawal due to lack of efficacy	Withdrav events, T Ulcer (en def:≥3mr Total car thrombot		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Valdecoxib	Placebo	NSAID	Efficacy+	Safety+		
Moskowitz 2003, Prizer Study 143	OA (not stated)	10mg per day (10mg od) (n=212)	n=110	Rofecoxib 25mg per day (25mg od) (n=208)	Patient's assessment of OA pain (100 mm VAS), Patient's assessment of pain on walking (100 mm VAS), WOMAC physical function, WOMAC stiffness, Patient's global assessment of arthritis, Withdrawal due to lack of efficacy	Withdraw events, T Dyspepsi infarctior severe, T		
Pfizer Study 063	OA (hip)	10mg per day (10mg od) (n=259) 20mg per day (20mg od) (n=261)	-	Diclofenac 150mg per day (75mg bd) (n=262)	Patients assessment of arthritis pain (VAS), patient's global assessment of arthritis, withdrawal due to lack of efficacy	POBs, dy myocardi SE, withc withdraw		
Pfizer Study 047	RA & OA (not stated)	40mg per day (20mg bd) (n=399) 80mg per day (40mg bd) (n=404)	-	Naproxen 1000mg per day (500mg bd) (n=415)	Patient's global assessment, Withdrawal due to lack of efficacy	Total wit Dyspepsi infarctior cardiovas Total AE to GI AE		
Bensen 2002, Pfizer Study 60 [257]	RA	10mg per day (10mg od) (n=209) 20mg per day (20mg od) (n=212) 40mg per day (40mg od) (n=221)	n=222	Naproxen 1000mg per day (1000mg od) (n=226)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Dyspepsi cardiovas Total AE		
Pavelka 2003 Pfizer Study 62	RA	20mg per day (20mg od) (n=246) 40mg per day (40mg od) (n=237)	-	Diclofenac 150mg per day (150mg od) (n=239)	Pain (VAS 100 mm), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (en ≥3mm) (Duodena Gastrodu (clinical Dyspepsi Withdraw		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		Valdecoxib	Placebo	NSAID	Efficacy+	Safety+		
Pfizer Study 016	RA	2.5mg per day (1.25mg bd), 5mg per day (2.5mg bd), 10mg per day (5mg bd), 20mg per day (10mg bd), 10mg qd (n=678) (total number of patients on all drugs)	n=678 (total number of patients on all drugs)	Naproxen 1000mg per day (500mg bd) (n=678) (total number of patients on all drugs)	Patient's assessment of pain (VAS), Functional status (e.g. WOMAC), Patient's global assessment of disease activity (VAS), Withdrawal due to lack of efficacy	Total wit		
Pfizer Study 061	RA	10mg per day (10mg od) (n=226) 20mg per day (20mg od) (n=219) 40mg per day (40mg od) (n=209)	n=220	Naproxen 1000mg per day (500mg bd) (n=219)	Patient's assessment of pain (VAS), Patient's global assessment of disease activity, Withdrawal due to lack of efficacy	Total wit PUB, Dy Myocard Total AE Withdraw		

4.8.4 Assessment of valdecoxib efficacy

Efficacy results across trials are summarised in Table 42, pg 115.

Patient's assessment of arthritis pain
Valdecoxib has equivalent pain relief effect to non-selective NSAIDs at licensed doses. This effect appeared to vary across dose and indication

Patient's assessment of global efficacy
Valdecoxib was mariginally less effective than non-selective NSAIDs. These differences were observed across various doses.

ACR-20 responder
Valdecoxib and non-selective NSAIDs led to similar ACR-20 responses.

Withdrawals due to lack of efficacy
Significantly more patients people on valdecoxib withdrew from lack of efficacy compared to non-selective NSAIDs. Significant differences were noted between valdecoxib 10 mg and non-selective NSAIDs in OA patients, but not at higher doses or in RA trials.

Table 39: Summary of efficacy results of valdecoxib versus placebo and NSAIDs

	Placebo				NS			
	VAS pain difference mean (95% CI)	**Global efficacy difference mean (95% CI)**	**ACR RR**	**Withdrawals due to lack of efficacy RR**	**VAS pain difference mean (95% CI)**	**Global efficacy difference mean (95% CI)**		
10 mg	*-10.05 (-13.98 to -6.13) [5]**	*CiC removed) [1]*	*1.41 (1.20 to 1.66) [3]*	*0.50 (0.39 to 0.63) [8]**	*3.20 (0.81 to 5.58) [5]*	*0.23 (0.12 to 0.34) [2]*		
20 mg	*-10.20 (-15.73 to -4.67) [4] **	*- CiC removed [1]*	*1.42 (1.21 to 1.67) [3]*	*0.50 (0.42 to 0.59) [6]*	*2.81 (0.31 to 5.30) [5]*	*0.20 (0.09 to 0.31) [2]*		
>20 mg	*-CiC removed [1]*	*CiC removed) [1]*	*1.48 (1.26 to 1.76) [2]*	*0.55 (0.45 to 0.67) [2]*	*CiC removed*) [1]	*CiC removed [1]*		
OA only	*-11.39 (-18.06 to -4.72) [3] **	No trials	No trials	*0.39 (0.24 to 0.63) [5]**	-6.05 (-18.28 to 6.17) [3]*	*CiC removed [1]*		
RA only	*-9.11 (-12.67 to -5.55) [2]*	*CiC removed [1]*	*1.43 (1.24 to 1.64) [3]*	*0.56 (0.49 to 0.64) [3]*	*4.64 (1.11 to 8.18) [2]*	*CiC removed) [1]*		
All trials	**-10.01 (-13.94 TO-6.09) [5]***	*CiC removed**) [1]***	***1.43 (1.24 to 1.64) [3]***	***0.49 (0.39 to 0.61) [8] ****	***-1.89 (-10.71 to 6.93) [5]****	***0.22 (0.139 to 0.32) [2]***		

*: significant (P≤0.01) heterogeneity – random effects meta-analysis

4.8.5 Valdecoxib tolerability

Adverse events

The occurrence of total adverse events and GI adverse events was similar for valdecoxib and placebo but patients treated with valdecoxib 20 mg or higher had a significantly higher risk of adverse events. Valdecoxib treatment at supra-license doses (>20 mg) resulted in significantly more GI adverse events compared to placebo. Valdecoxib caused significantly fewer GI adverse events and adverse events overall compared with non-selective NSAIDs. These differences were observed across all doses and for OA and RA.

Table 40: Summary of adverse events for valdecoxib versus placebo & NSAIDs

	Placebo Relative risk (95% CI) [N trials]	**NSAIDs Relative risk (95% CI) [N trials]**
All adverse events		
10mg	1.07 (0.99 to 1.15) [8]	*0.88 (0.83 to 0.94) [8]*
20 mg	*1.15 (1.06 to 1.25) [6]*	*0.90 (0.86 to 0.96) [8]*
> 20 mg	*1.25 (1.10 to 1.42) [2]*	*0.94 (0.90 to 0.99) [4]*
OA only	1.02 (0.94 to 1.11) [5]	*0.88 (0.82 to 0.93) [5]*
RA only	1.03 (0.71 to 1.49) [3]*	0.83 (0.62 to 1.11) [4] *
All trials	**1.00 (0.87 to 1.15) [8]***	***0.87 (0.78 to 0.97) [10] ****
GI adverse events		
10mg	1.15 (0.99 to 1.34) [6]	*0.78 (0.69 to 0.88) [6]*
20 mg	1.09 (0.92 to 1.29) [5]	*0.73 (0.66 to 0.82) [7]*
> 20 mg	*1.33 (1.09 to 1.64) [2]*	*0.84 (0.76 to 0.92) [4]*
OA only	1.05 (0.72 to 1.52) [3]*	*0.84 (0.71 to 0.98) [2]*
RA only	0.98 (0.71 to 1.36) [3]*	*0.69 (0.55 to 0.87) [4] **
All trials	**1.02 (0.82 to 1.26) [6] ***	***0.74 (0.66 to 0.84) [8] ****

*: significant (P≤0.01) heterogeneity – random effects meta-analysis

Withdrawals

Withdrawals from all adverse events and from GI adverse events were similar for valdecoxib and placebo, and both had significantly fewer withdrawals from these events compared with non-selective NSAIDs. Withdrawals for any reason were significantly less likely with valdecoxib than with either placebo or non-selective NSAIDs.

Table 41: Summary of withdrawals for valdecoxib versus placebo & NSAIDs

	Placebo **Relative risk (95% CI)** **[N trials]**	**NSAIDs** **Relative risk** **(95% CI) [N trials]**
All adverse event withdrawals		
10mg	1.17 (0.87 to 1.58) [8]	*0.65 (0.51 to 0.81) [8]*
20 mg	1.04 (0.74 to 1.46) [6]	*0.58 (0.46 to 0.73) [8]*
> 20 mg	1.73 (0.99 to 3.00) [2]	0.91 (0.73 to 1.13) [4]
OA only	1.07 (0.77 to 1.49) [5]	*0.57 (0.46 to 0.71) [5]*
RA only	1.17 (0.75 to 1.82) [3]	0.73 (0.39 to 1.39) [4]*
All trials	**1.11 (0.85 to 1.44) [8]**	***0.66 (0.51 to 0.86) [10] ****
All GI withdrawals		
10mg	1.61 (0.79 to 3.28) [4]	*0.44 (0.29 to 0.68) [5]*
20 mg	0.91 (0.37 to 2.28) [3]	*0.35 (0.23 to 0.54) [5]*
> 20 mg	CiC removed [1]	*0.56 (0.41 to 0.77) [3]*
OA only	1.43 (0.53 to 3.82) [2]	*0.36 (0.23 to 0.57) [3]*
RA only	1.05 (0.44 to 2.50) [2]	*0.40 (0.27 to 0.59) [3]*
All trials	**1.20 (0.63 to 2.30) [4]**	***0.47 (0.38 to 0.59) [7]***
All withdrawals		
10mg	0.66 (0.59 to 0.73) [8]	0.99 (0.89 to 1.10) [8]
20 mg	0.64 (0.54 to 0.77) [6]*	0.90 (0.76 to 1.08) [8]*
> 20 mg	0.65 (0.56 to 0.75) [2]	0.94 (0.84 to 1.06) [4]
OA only	0.58 (0.43 to 0.77) [5]*	0.86 (0.71 to 1.04) [5]*
RA only	0.56 (0.38 to 0.84) [3]*	0.88 (0.68 to 1.13) [4]*
All trials	**0.57 (0.45 to 0.71) [8]***	***0.88 (0.77 to 0.99) [10] ****

*: significant (P≤0.01) heterogeneity – random effects meta-analysis

4.8.6 Safety of valdecoxib

Endoscopic GI ulcers
Valdecoxib caused significantly fewer endoscopic ulcers compared with non-selective NSAIDs.

Clinical UGI events (PUBs) and complicated UGI events (POBs)
Valdecoxib significantly reduced the risk of PUBs (RR: 0.12, 0.03-0.59; NNT: 84, 76-179) and POBs (RR: 0.38, 0.17-0.86; NNT: 162, 121-719) compared with non-selective NSAIDs.

Myocardial infarctions and cardiovascular thrombotic events
Too few serious cardiovascular events occurred in valdecoxib trials to draw any sensible conclusions. Pooled results showed two events in valdecoxib patients compared with four events in non-selective NSAID arms of trials (RR: 0.23, 0.06-0.90; NNT: 184, 151-1420). Serious cardiovascular thrombotic events were also not well reported.

Table 42: Summary of endoscopic GI ulcers and clinical and complicated UGI events (PUBs and POBs) for valdecoxib versus placebo or NSAIDs

	Placebo Relative risk (95% CI) [N trials]	**NSAIDs Relative risk (95% CI) [N trials]**
Endoscopic GI ulcers		
10mg	0.73 (0.35 to 1.53) [2]	*0.28 (0.15 to 0.51) [2]*
20 mg	0.99 (0.51 to 1.93) [2]	*0.35 (0.24 to 0.53) [3]*
> 20 mg	Not reported	*0.35 (0.24 to 0.51) [2]*
OA only	0.87 (0.48 to 1.57) [2]	*0.32 (0.21 to 0.49) [2]*
RA only	Not reported	CiC removed *[1]*
All trials	0.87 (0.48 to 1.57) [2]	***0.32 (0.25 to 0.41) [4]***
POBs		
10mg	‡	0.26 (0.04 to 1.54) [3]
20 mg	¶	0.61 (0.20 to 1.86) [4]
> 20 mg	CiC removed [1]	0.41 (0.13 to 1.30) [3]
OA only	¶ CiC removed [1]	0.62 (0.13 to 2.89) [2]
RA only	CiC removed [1] ¶	0.24 (0.05 to 1.00) [2]
All trials		***0.38 (0.17 to 0.86) [5]***
PUBs		
10mg	¶	0.14 (0.02 to 1.30) [2]
20 mg	¶	0.20 (0.02 to 1.68) [2]
> 20 mg	CiC removed [1]	CiC removed [1]
OA only	†	CiC removed [1]
RA only	CiC removed [1]	CiC removed *[1]*
All trials	CiC removed [1] †	***0.12 (0.03 to 0.59) [2]***

*: significant (P≤0.01) heterogeneity – random effects meta-analysis; † one trial reported zero events in both arms.
¶ two trials reported zero events in both arms. ‡ three trials reported zero events in both arms.

Figure 14: Risk of POBs with valdecoxib (all doses) vs NSAIDs (all drugs) [figure CIC]

CiC figure removed because of the confidential nature of some studies

Figure 15: Risk of PUBs with valdecoxib (all doses) vs NSAIDs (all drugs) [figure CIC]

CiC figure removed due to the confidential nature of some studies

Table 43: Summary of myocardial infarction and serious thrombotic events for valdecoxib versus placebo or NSAIDs

	Placebo Relative risk (95% CI) [N trials]	**NSAIDs Relative risk (95% CI) [N trials]**
MI		
10mg	1.02 (0.15 to 7.04) [2] ¶	0.48 (0.11 to 2.09) [3] †
20 mg	CiC removed [1] ¶	0.20 (0.02 to 1.71) [2] ¶
> 20 mg	CiC removed [1]	CiC removed [1]
OA only	¶	CiC removed [1] †
RA only	0.46 (0.09 to 2.39) [2]	0.46 (0.09 to 2.39) [2]
All trials	**0.46 (0.09 to 2.39) [2] ¶**	***0.23 (0.06 to 0.90) [3]*** **†**
Serious CV thrombotic events		
10mg	CiC removed [1] ¶	†
20 mg	CiC removed [1] †	†
> 20 mg	CiC removed [1]	No trials
OA only	¶	†
RA only	CiC removed) [1]	No trials
All trials	CiC removed **[1]** ¶	**†**

† one trial reported zero events in both arms. ¶ two trials reported zero events in both arms. ‡ three trials reported zero events in both arms.

Figure 16: Risk of MI with valdecoxib (all doses) vs NSAIDs (all drugs) [figure CIC]

CiC figure removed due to the confidential nature of some studies

4.8.7 Subgroup analyses

Pavelka and colleagues[258] reported that H. pylori status, low-dose aspirin, and age had no significant effect on gastro-duodenal ulcer rates between valdecoxib 20 mg, 40 mg and diclofenac150 mg treatment groups (P≥0.51) but no details were given. Sikes et al[256] and Pfizer Study 047[259] provided numerical data. Pooled results from these two trials are summarised in Table 44, pg 118. No trials reported subgroup analyses for clinical UGI events, complicated UGI events or serious cardiovascular events.

H. pylori status

Both studies reported non-significant trend towards higher endoscopic ulcer rates among patients who were tested *H. pylori* positive. The risk reduction for patients treated with valdecoxib compared with non-selective NSAIDs does not appear to be affected by *H. pylori* status.

Low dose aspirin

No consistent results were observed; Sikes and colleagues found that aspirin increased endoscopic gastroduodenal ulcer rates in with valdecoxib 10 mg, diclofenac and ibuprofen, but not with valdecoxib 20 mg and placebo [CiC removed].

Age

One of the studies[256,259] reported a higher incidence of endoscopic ulcers among patients aged 65 years and over compared with younger patients [the other studies was submitted as CiC and has been removed]. The risk reduction for patients treated with valdecoxib compared with non-selective NSAIDs does not appear to be affected by age.

Prior GI ulcers

No consistent result was reported: Sikes and colleagues found that a prior ulcer history had no effect on ulcer incidence in any treatment group; [CiC removed].

Table 44: Endoscopic ulcers for valdecoxib vs non-selective NSAIDs by sub-groups

Subgroup [N trials]	Pooled events Valdecoxib vs NSAID	Pooled relative risk (95% CI)**	Comparative relative risk
***H. pylori* status**			
Positive [2]	16/221 vs 39/175	*0.31 (0.18 to 0.54)*	0.97
Negative [2]	37/715 vs 72/477	*0.32 (0.21 to 0.47)*	
Low dose aspirin			
User [2]	21/132 vs 27/118	0.72 (0.18 to 2.80)*	3.00
Non user [2]	35/936 vs 88/602	*0.24 (0.16 to 0.35)*	
Age			
≥65 yrs [2]	32/329 vs 53/237	*0.39 (0.26 to 0.60)*	1.63
< 65yrs [2]	24/739 vs 62/483	*0.24 (0.15 to 0.38)*	
Prior GI ulcer			
Present [1]	CiC removed	CiC removed	CiC removed
Not present [1]	CiC removed	CiC removed	

*Significant heterogeneity – pooled by random effects; **Relative risk valdecoxib vs non-selective NSAIDs

4.8.8 Impact of concomitant gastroprotective agents

No relevant trials identified.

4.8.9 Summary

Based on the systematic review and meta-analysis, it is concluded that:

- 11 RCTs were included. Studies compared valdeoxib (200 to 800mg/day) to either placebo or non-selective NSAIDs (naproxen or diclofenac).
- Valdecoxib of equivalent or magnially inferior, particularly in RA patients, than non-selective NSAIDs.
- Valdecoxib is associated with significantly fewer total and GI adverse events, and withdrawals as a result of adverse events than non-selective NSAIDs.
- Valdecoxib is associated with significantly fewer endoscopic ulcers compared with non-selective NSAIDs.
- Based on short-term trials (6-month or less) valdecoxib is associated with fewer clinical and complicated UGI events compared with non-selective NSAIDs.
- There is insufficient data on the occurrence of MIs, the effect of H. pylori, aspirin, age, anticogulants, concomitant low dose aspirin to draw any conclusions about the benefits or hazards of valdecoxib. Also no trial compared valdecoxib with non-selective NSAIDs with a gastro-proctective agent.

4.9 Direct comparisons of COX-2 selective NSAIDs

4.9.1 Description of included trials, patient characteristics and trial quality

Direct comparisons of two COX-2 selective NSAIDs are reported in a small number of trials: six compared celecoxib with rofecoxib in OA and RA over 6 to 12 weeks. Patients were randomised to celecoxib 200 mg or rofecoxib 25 mg per day and one trial also included a rofecoxib 12.5 mg arm. A further trial compared valdecoxib (10mg per day; n=212) to rofecoxib (25mg per day; n=208) in patients with RA over 2 weeks (Moskowtiz, 2003 - P0143).

All seven included trials scored 5 on the Jadad scale indicating high quality.
All trials were of short duration (less than 3 months) and relatively few patients have been studied and no serious GI events reported.

Table 45: Characteristic and quality of included head to head OA trials

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		COX-2s	Placebo	NSAID	Efficacy+	Safety+		
McKenna 2001b, Pfizer Study 152 [145]	OA (knee)	**Celecoxib** 200mg per day (200mg od) (n=63) **Rofecoxib** 25mg per day (25mg od) (n=59)	n=60	-	Pain (VAS), Withdrawal due to lack of efficacy	Withdraw events, T Dyspepsi severe, M infarctior cardiovas Total AE Withdraw		
Whelton 2001, SUCCESS-VI, Pfizer Study 149 [260]	OA (hip, hand, knee)	**Celecoxib** 200mg per day (200mg od) (n=411) **Rofecoxib** 25mg per day (25mg od) (n=399)	n=220	-	-	Withdraw events, D AE sever		
Whelton 2002a, SUCCESS VII, Pfizer Study 181 [261]	OA (hip, knee, hand)	**Celecoxib** 200mg per day (200mg od) (n=549) **Rofecoxib** 25mg per day (25mg od) (n=543)	-	-	Withdrawal due to lack of efficacy	Withdraw events, T Total AE		
Gibofsky 2003, Pfizer Study 003 [150]	OA (knee)	**Celecoxib** 200mg per day (200mg od) (n=189) **Rofecoxib** 25mg per day (25mg od) (n=190)	n=96	-	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Dyspepsi severe, T		
Sowers 2003, CRESECENT, Pfizer Study 002 [262] **(Pfizer 2004 submission)**	OA (hip, knee)	**Celecoxib** 200mg per day (200mg od) (n=136) **Rofecoxib** 25mg per day (25mg od) (n=138)	-	Naproxen 1000mg per day (500mg bd)	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Total wit Dyspepsi infarctior cardiovas Total AE		

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes			
		COX-2s	Placebo	NSAID	Efficacy+	Safety+		
Geba 2002, VACT-1 [263]	OA (knee)	**Celecoxib** 200mg per day (200mg od) (n=97) **Rofecoxib** 12.5mg per day (12.5mg od) (n=96) 25mg per day (25mg od) (n=95)	-	Paracetamol 4g per day (1g qds) (n=94)	Pain (WOMAC), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Ulcer (en or sympt Dyspepsi infarctior cardiovas Total AE to GI AE		
Moskowitz (2003) Pfizer Study 143, [264] **(Pfizer 2004 submission)**	OA (knee)	**Valdecoxib** 10mg per day (10mg od) (n=212) **Rofecoxib** 25mg per day (25mg od) (n=208)	n=110	-	Pain (VAS), Patient's global assessment, Withdrawal due to lack of efficacy	Withdraw events, T Dyspepsi infarctior cardiovas Total AE		

4.9.2 Efficacy

Patient's assessment of arthritis pain
Celecoxib and rofecoxib reduced pain, assessed by VAS in 4 of 6 trials, equally well (see Figure 17). Similarly valdecoxib and rofecoxib gave similar degrees of pain relief (VAS -37.8, SD 2.0 versus –40.7, SD 2.0).

Figure 17: Comparison of change in VAS pain between celecoxib (200mg/day) and rofecoxib (12.5-25mg/day) [figure CIC except pooled esitmate]

[CiC figure removed due to the confidential nature of one of the studies]

Pooled estimate RR 0.85 (95% CI, -2.49, 4.20) in favour of rofecoxib.

Patient's assessment of global efficacy
[CiC removed]

ACR-20 responder
No trials reported ACR-20 response.

Withdrawal due to lack of efficacy
No significant difference in withdrawals due to lack of efficacy was found between celecoxib and rofecoxib in pooled analysis (see Figure 18).

Figure 18: Comparison of level of withdrawal due to lack of efficacy in celecoxib (200mg/day) and rofecoxib (12.5-25mg/day) [figure CIC except pooled estimate]

[CiC figure removed due to the confidential nature of some of the studies]

Pooled estimate RR 1.22 (95% CI, 0.75, 2.00) in favour of rofecoxib.

[CiC text removed related to withdrawls from celecoxib and rofecoxib due to lack of efficacy].

4.9.3 Tolerability

Total adverse events

There was no evidence of a difference in overall adverse events between celecoxib-treated and rofecoxib-treated patients (see Figure 19, pg 125).

[CiC removed – text related to adverse events with valdecoxib and rofecoxib]

GI adverse events

Overall there appeared to be no difference in the level of GI adverse events in celecoxib and rofecoxib groups (see Figure 20). However, one study of McKenna and colleagues (2001) did report a significantly lower level of GI adverse events with celecoxib (relative risk – CiC removed).

[CiC removed – text related to the incidence of GI specific adverse events with valdecoxib compared to rofecoxib.]

Figure 19: Comparison of overall adverse events with celecoxib (200mg/day) and rofecoxib (12.5-25mg/day) [figure CIC except pooled estimate]

[CiC figure removed due to the confidential nature of some of the studies]

Pooled estimate – RR 0.97 (95% CI, 0.91, 1.04) favouring celecoxib.

Figure 20: Comparison of GI adverse events with celecoxib (200mg/day) and rofecoxib (12.5-25mg/day) [figure CIC except pooled estimate]

[CiC figure removed due to the confidential nature of one of some of the studies].

Pooled estimate – RR 0.85 (95% CI, 0.51, 1.41)

Withdrawals due to adverse events
Overall, withdrawals due to adverse events appeared to equivalent between celecoxib and rofecoxib (see Figure 21). [CiC removed – text related to adverse event withdrawls with celecoxib compared to rofecoxib].

[CiC removed – text related to adverse event withdrawls in the valdecoxib vs. rofecoxib study].

Figure 21: Comparison of withdrawals due to adverse events with celecoxib (200mg/day) and rofecoxib (12.5-25mg/day) [figure CIC except pooled estimate]

[CiC figure removed due to the confidential nature of some of the studies]

Pooled estimate – RR 0.89 (95% CI, 0.67, 1.17) in favour of celecoxib.

Withdrawals due to GI events
The level of withdrawal due to GI-related adverse events appeared to equivalent between celecoxib and rofecoxib acoss the three trials where it was reported.

Figure 22: Comparison of withdrawals due to GI adverse events with celecoxib (200mg/day) and rofecoxib (25mg/day) [figure CIC except pooled estimate]

[CiC figure removed due to the confidential nature of some of the studies]

Pooled estimate – RR 0.75 (95% CI, 040, 1.43) in favour of celecoxib.

Withdrawals due to GI-specific adverse events were not reported in the valdecoxib versus rofecoxib trial.

4.9.4 Summary

Based on this systematic review and meta-analyses it is concluded that:

- A small number (n=7) of short-term (2 to 12 weeks) 'head-to-head' trials have directly compared COX-2 selective NSAIDs in OA and RA patients.
- These trials typically compared maximum licensed dose of rofecoxib (25mg/day) to either celecoxib (200mg/day) or valdecoxib (10mg/day), both at half of their maximum licensed doses. Only one trial (VACT-1) has included rofecoxib 12.5 mg/day.
- The efficacy and tolerability of rofecoxib appeared to be similar to both celecoxib and valdecoxib but, in view of the limited evidence base and because these comparisons are underpowered and at potentially non-equivalent doses, caution is needed in this interpretation.
- There is no evidence from direct head-to-head trials in order to comment on the relative safety of COX-2s in terms of their serious GI (POBs or PUBs) or cardiovascular effects.

5 ECONOMIC ANALYSIS

5.1 Introduction

The aim of this section is to assess the cost-effectiveness of celecoxib, rofecoxib, etodolac, meloxicam, etoricoxib and valdecoxib for OA or RA from a National Health Services (NHS) perspective. We include a systematic review of the published literature on the cost-effectiveness of COX-2 selective NSAIDs, a review of economic analyses submitted by manufacturers, and a description of our own modelling and economic analyses.

5.2 Systematic review of published cost effectiveness literature

5.2.1 Methods for the systematic review

A systematic literature search was undertaken to identify economic evaluations where the cost-effectiveness of one or more of the COX-2 drugs was investigated.

For all COX-2 selective NSAIDs, the searches for clinical effectiveness were amplified to identify any existing economic models and information on costs, cost effectiveness and quality of life from the following sources:

- Bibliographic databases: MEDLINE, pre-MEDLINE, EMBASE, NHS EED, DARE, HEED.
- Internet sites of national economic units
- Internet sites of regulating authorities, e.g. FDA, EMEA

Databases were searched from the inception date of the databases for all drugs.

Full details of the search terms used and the overall search strategy are in Appendix 2, pg 194.

The inclusion and exclusion criteria applied for the economic searches are shown in Table 46.

Table 46: Inclusion criteria for the review on cost-effectiveness

Study design	Cost-consequence analysis, cost-minimisation analysis, cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis; cost studies (UK only), quality of life studies
Population	People with OA or RA; other forms of arthritis are excluded
Intervention	Celecoxib, rofecoxib, meloxicam, etodolac, etoricoxib and valdecoxib, with or without aspirin
Comparator	Non-COX-2 NSAIDs with or without gastroprotective agents, COX-2 selective NSAIDs with or without gastroprotective agents
Outcome	Quality of life estimates, cost estimates, cost-effectiveness

An experienced health economist (SB) identified included studies by applying inclusion and exclusion criteria and screening titles, abstracts and full text, if appropriate, of bibliographic searches.

A reviewer using a pre-designed data extraction form extracted data from included studies. Data have been extracted on the following:

- Study characteristics such as form of economic analysis, population, interventions, comparators, perspective, time horizon, and modelling used.
- Effectiveness and cost parameters such as effectiveness data, health state valuations (utilities), resource use data, unit cost data, price year, discounting, and key assumptions.
- Results and sensitivity analyses.

These characteristics and main results of included economic evaluations are summarised in a table. The quality of included studies was assessed using the Drummond and Jefferson checklist.[265] The study question, selection of alternatives, form of evaluation, effectiveness data, costs, benefit measurement and valuation, decision modelling, discounting, allowance for uncertainty and presentation of results were all evaluated as part of this process.

5.2.2 Results of the cost-effectiveness systematic review

Fifteen published studies meeting the criteria for inclusion were identified. In addition, three manufacturers (Boehringer Ingelheim, Merck, Sharp & Dohme and Pfizer submitted economic analyses and models. These submissions are reviewed in detail in section 2.3, pg 19, of this chapter).

Details of the 15 studies (presented using a simplified version of the Drummond & Jefferson checklist[266]) are reported in Appendix 7, pg 262. Of these 15, 3 were sponsored by Merck and considered rofecoxib only in comparison with an unnamed non-selective or conventional NSAID (see Table 47). All 3 studies were cost-effectiveness analyses, with the cost effectiveness ratio either being in the form of cost per PUB avoided or cost per life year gained. Results universally indicated that the incremental cost of rofecoxib is positive; but, all the authors concluded that the associated benefits leads supported more widespread use of rofecoxib in OA. All three studies used a very similar simple decision tree model structure. These models did not include the possibility of drug-related MI.

Table 47: Published rofecoxib economic analyses

Study	Sponsor	Patient group	Comparator(s)	Base case ICER
Marshall et al (2001)[267]	Merck	OA	Non-selective NSAID	Can$2,000 per PUB avoided
Pellissier et al (2001)[268]	Merck	OA	Non-selective NSAID	US$4,700 per PUB avoided US$18,600 per life year saved
Moore et al (2001)[269]	Merck	OA	Conventional NSAIDs	UK£10,700 per PUB avoided UK£15,600 per life year saved

Five of the 15 identified published studies report an economic analysis of celecoxib alone (see Table 48, pg 130); 4 of which were sponsored by the manufacturer (either Pfizer or Pharmacia). All 4 of the company-sponsored analyses used a simple decision tree that was either the same as the Arthritis Cost Consequences Evaluation System (ACCES) model (see description of Pfizer submission for more details) or was a slight modification of it. Against the range of comparators explored (ranging from conventional NSAID as monotherapy to NSAIDs with various GPAs), the most common result was that celecoxib dominated the alternatives; so, celocoxib costs less and was more effective. Unsurprisingly, these reports recommended more

widespread use of celecoxib in people with arthritis. ICERs in two other comparisons of celecoxib with NSAID monotherapy, Zabinski et al (2001)[270] and Haglund & Svarvar (2000)[271], were Can$1,800 per GI event avoided and SEK780 per GI event avoided, respectively.

A study sponsored by US Veterans Affairs came to a more cautious conclusion: that celecoxib is only cost-effective in OA patients with a high baseline risk of UGI events. This was again a decision tree model although the detail of the model was not reported in the paper. None of the 5 models of celecoxib, described above, considered MIs in their analyses.

Table 48: Published celecoxib economic analysis

Study	Sponsor	Patient group	Comparator(s)	Base case ICER
Chancellor et al (2001)[272]	Pharmacia	Arthritis	5 strategies: - NSAID alone - NSAID + PPI - NSAID + H_2RA - NSAID + misoprostol - Diclofenac/ misoprostol	Celecoxib dominant against all comparators (i.e. lower cost and fewer GI events)
Zabinski et al (2001)[270]	Pfizer and Pharmacia	OA or RA	5 strategies: - NSAID alone - NSAID + PPI - NSAID + H_2RA - NSAID + misoprostol - Diclofenac/ misoprostol	Celecoxib vs NSAID alone: Can$1,800 per serious GI event avoided Celecoxib vs all other strategies: celecoxib dominant
Svarvar & Aly (2000)[273]	Pfizer	OA and RA analysed separately	2 comparators: - NSAID monotherapy - Average NSAID use in Norway	For both OA and RA, celecoxib dominant against both comparators
Haglund & Svarvar (2000)[271]	Pfizer	OA or RA analysed separately	2 comparators: - NSAID monotherapy - Average NSAID use in Sweden	For OA, celecoxib dominant against both comparators For RA, celecoxib vs NSAID monotherapy: SEK780 per GI event avoided For RA, celecoxib vs 'average basket': celecoxib dominant
El-Serag (2002)[274]	US Veterans Affairs	OA	7 strategies: - ibuprofen - ibuprofen + PPI - ibuprofen + misoprostol - HP treatment + ibuprofen - HP treatment + ibuprofen + PPI - HP treatment + ibuprofen + misoprostol - HP treatment + celecoxib	With 2.5% baseline risk of clinical UGI event with conventional NSAID, US$35,200 per clinical UGI event avoided (celecoxib vs ibuprofen) With 6.5% baseline risk of clinical UGI event with conventional NSAID, celecoxib dominates

A further 5 cost-effectiveness studies (all published in 2003) considered both celecoxib and rofecoxib, none of which was funded by a drug manufacturer (see Table 49, pg 131). All of these analyses came to results that were less attractive for COX-2 selective NSAIDs. Most of these studies considered a longer time horizon; for example, lifetime in the case of Spiegel, and 5 years in the cases of Maetzel and Rafter (see Appendix 7, pg 262).

Table 49: Published rofecoxib and celecoxib economic analyses

Study	Sponsor	Patient group	Comparator(s)	Base case ICER
Spiegel et al (2003)[275]	US National Institute for Health and Veterans Affairs	OA or RA	Nonselective NSAID (i.e. naproxen)	For the average patient, US$275,800 per QALY gained For patients who have had a previous ulcer haemorrhage, US$55,800 per QALY gained
Maetzel (2003)[276]	Canadian Co-ordinating Office for HTA	OA or RA	For average risk patients: - naproxen (vs rofecoxib) - diclofenac (vs celecoxib) - ibuprofen (vs celecoxib) For high risk patients, all comparators also included the addition of PPIs	For average risk patients: - Can$271,000 per QALY gained (rofecoxib vs naproxen) - Can$125,000 per QALY gained (celecoxib vs diclofenac) For high risk patients: - Rofecoxib dominates naproxen + PPI - Celecoxib dominates ibuprofen + PPI - Can$271,000 per QALY gained (celecoxib vs diclofenac + PPI)
Rafter (2003)[277]	Accident Compensation Corporation & Australasian Faculty of Public Health Medicine	OA or RA	3 comparators: - naproxen (vs rofecoxib) - diclofenac (vs celecoxib) - ibuprofen (vs celecoxib)	Naproxen dominates rofecoxib Diclofenac dominates celecoxib Celecoxib vs ibuprofen: - NZ$482,000 per QALY gained (average risk patients) - NZ$88,000 per QALY gained (high risk)
Kamath et al (2003)[278]	McNeil Consumer Healthcare	Symptomatic knee OA	3 comparators: - high dose acetaminophen - ibuprofen - ibuprofen + misoprostol	Acetaminophen dominant against all comparators (i.e. lower cost and fewer GI events)
Bae et al (2003)[279]	Korean Ministry of Health & Arthritis Foundation	RA	2 comparators: - corticosteroids - NSAIDs	US$51,700 per QALY gained (COX-2 vs NSAID) US$137,000 per QALY gained (COX-2 vs corticosteroids)

Spiegel and colleagues (2003)[275] did not distinguish between rofecoxib and celecoxib and assumed they had the same cost and benefit characteristics. They focused on patients with

either OA or RA and used a decision tree model. Detailed base case results found are shown in Table 50, costs and QALY estimates are for an *average* patient over a lifetime.

Table 50: Base case study results – Spiegel et al (2003)

		Cost ($)	QALYs	ICER (US$)
Base case	Naproxen	4859	15.2613	
	Coxib	16443	15.3033	275,800
Including cardiovascular events	Naproxen	2037	15.2539	
	Coxib	16620	15.2832	395,000
High-risk cohort (previous ulcer haemorrhage)	Naproxen	14294	14.7235	
	Coxib	19015	14.8081	55,800

Whilst the ICER for the strategy of restricting use of COX-2s to patients who had a previous ulcer haemorrhage was more attractive (US$55,800 per QALY gained) than unrestricted use (US$275,800 per QALY gained). Nevertheless, the inclusion of cardiovascular events would result in COX-2 selective NSAIDs being less cost-effective.

Maetzel (2003)[276] and Rafter (2003)[277] came to the same broad result. They both used a very similar Markov model (originally developed by Maetzel), and considered the use of COX-2 selective NSAIDs in both OA and RA. The detailed base case results reported by Maetzel (2003)[276] are shown in Table 51. The costs and QALY estimates are for the average patient over a 5-year time horizon.

Table 51: Base case study results – Maetzel (2003)

		Costs (Can$)	Complicated UGI events	QALYs	ICER (cost/QALY gained)
Average risk	Naproxen	1576	7.70	2.8938	
	Rofecoxib	3173	3.39	2.8997	271,000
	Ibuprofen	1141	6.36	2.8990	
	Diclofenac	2570	2.68	2.9104	125,000
	Celecoxib	3371	2.48	2.9095	Dominated by diclofenac
High risk	Rofecoxib	4090	7.45	2.8851	
	Naproxen + PPI	4766	11.31	2.8816	Dominated by rofecoxib
	Rofecoxib + PPI	6486	5.13	2.8936	281,000
	Celecoxib	4327	5.54	2.9003	
	Ibuprofen + PPI	4414	9.49	2.8894	Dominated by celecoxib
	Diclofenac + PPI	5980	4.11	2.9064	271,000
	Celecoxib + PPI	6746	3.81	2.9057	Dominated by diclofenac

Maetzel and colleagues' results support the use of rofecoxib and celecoxib only in high-risk patients with a previous clinical UGI event but Rafter (2003) concludes that neither drug represents value for money: both studies explicitly considered cardiovascular events. Kamath et al (2003)[278], using a decision tree, did not find any support for the use of rofecoxib and celecoxib in patients with knee OA.. Bae and colleagues (2003)[279] used a Markov model and found that comparing COX-2 selective NSAIDs versus a standard NSAID in RA cost US$51,700 per QALY gained.

A study of meloxicam, Tavakoli (2003)[280], that appears not to have been funded by a manufacturer of meloxicam is summarised in Table 52. This analysis used a simple decision tree and found that meloxicam dominated the alternatives (diclofenac and piroxicam). Cardiovascular events were included in this analysis.

Fendrick et al (2002)[281] considered an unnamed COX-2 (see Table 52) and from an analysis of a Markov model concluded that whilst the unrestricted use of COX-2 selective NSAIDs has the potential to provide important clinical benefit in long-term users of NSAIDs, there is a considerable incremental cost. Cardiovascular events were not included in this analysis.

Table 52: Published Meloxicam economic analysis and published economic analysis of unnamed COX-2 selective NSAIDs

Study	Sponsor	Patient group	Comparator(s)	Base case ICER
Tavakoli (2003)[280]	None	OA	Meloxicam compared with: - diclofenac - piroxicam	Meloxicam dominant against both comparators
Fendrick et al (2002)[281]	SKB ('unrestricted grant')	Long-term users of NSAIDs	2 strategies compared: - generic NSAID used initially, with safer NSAID used for patients with GI events or intolerance - safer NSAIDs used first line for all patients	For first line use: US$31,900 per symptomatic ulcer avoided US$56,700 per complicated ulcer avoided

5.2.3 Summary

- Results of many economic evaluation of COX-2 selective and non-selective NSAIDs are highly variable: some analyses suggest dominance and so support the wide use of COX-2 selective NSAIDs; others report very high ICERs and conclude that use of COX-2 selective NSAIDs cannot be considered an appropriate use of health care resources.

- Many of the previous analyses are based on clinical estimates that are derived from single trials, or a small number of trials, rather than a formal systematic review and meta-analysis of the evidence.

- Drug manufacturers have sponsored a majority of published analyses; however, government agencies and others have also published economic evaluations of COX-2

selective NSAIDs. Studies not supported by the drug manufacturers are considerably less favourable to COX-2 selective NSAIDs.

- Virtually all economic analyses use a decision analytic model. Published models vary in some important aspects; for example, whether switching of therapy is considered, timescale, nature of events considered, and so on. This makes direct comparison difficult but it does appear that those explicitly iincluding cardiovascular events found COX-2 selective NSAIDs less attractive.

- Most analyses have modelled costs and benefits over a relatively short period (usually between 6 and 12 months) and their results tend to support the widespread use of COX_2 selective NSAIDs. Where a longer time horizon has been modelled (e.g. between 5 years and patient lifetime) cost-effectiveness ratios are considerably higher.

- Analyses that consider restricting the use of COX-2 selective NSAIDs to 'high risk' patient's results are in favour of restriction.

5.3 Review of industry cost effectiveness submissions

A detailed summary of the economic analyses and models included in the company submissions has been undertaken and is reported in this section. Table 53 shows the information that was presented by the companies; no economic analysis for etodolac is available. Analyses presented by Pfizer, MSD and Boehringer Ingelheim will be discussed in turn.

Table 53: Cost-effectiveness information in company submissions

Manufacturer	Drug	Economic analysis included in submission?	Electronic files of model provided?
Pfizer	Celecoxib Valdecoxib	Yes	Yes
Merck Sharp & Dohme	Rofecoxib Etoricoxib	Yes	Yes
Boehringer Ingelheim	Meloxicam	Yes	Yes
Shire	Etodolac	No	No

An overview of the methods used in the economic analyses is presented in

Table 54, pg 136.

Table 54: Summary of methods used in industry economic analyses

Submission features	Pfizer	Merck Sharp & Dohme	Boehringer Ingelheim
COX-2s considered	Celecoxib Valdecoxib	Rofecoxib (12.5mg, 25mg and 50mg once daily) Etoricoxib (60mg, 90mg and 120mg once daily)	Meloxicam (7.5mg and 15mg once daily)
Comparison technologies	Non-selective NSAID alone Non-selective NSAID plus PPI Non-selective NSAID plus H_2A Arthrotec Non-selective NSAID plus misoprostol	Non-selective NSAIDs alone Non-selective NSAIDs plus PPIs Non-selective NSAIDs plus misoprostol Non-selective NSAIDs plus H_2As	Diclofenac retard (100mg once daily) Piroxicam (20mg once daily)
Patient characteristics	Patients with arthritis, following the failure of simple analgesia / paracetemol Average risk patient: age 62, no history of GI side effects or complications, no aspirin use and HAQ of 1 High risk patient: age 72, history of GI side effect, aspirin use and HAQ of 2	Patient with chronic OA / RA	Average patient with OA Patient with previous symptomatic ulcer (without PPI)
Form of economic analysis	Cost-effectiveness analysis (i.e. cost per life year saved)	Cost-utility analysis	Cost-utility analysis
Model used	Decision tree (based on ACCES model)	Decision tree	Markov model (based on Maetzel model)
Time horizon of model	1 year (but calculation of life years lost considered patient age and expected survival from actuarial life tables)	1 year (but calculation of life years lost from actuarial life tables)	5 years
Assumption concerning differential effectiveness / efficacy	Equal efficacy for all treatment arms	Equal efficacy for all treatment arms	Equal efficacy for all treatment arms

5.3.1 Pfizer submission

Celecoxib or valdecoxib are compared with a generic NSAID (a weighted average of NSAIDs used in the UK); patients with either OA or RA are considered. A direct comparison of celecoxib versus valdecoxib is not reported. Pfizer use the ACCESS decision tree, in line with most published economic analyses of celecoxib (supported by Pfizer). The model structure is shown in

Figure 23, pg 146. Patients move along the tree from left to right and events cover a 1-year time horizon but the calculation of life years gained is undertaken using UK actuarial life tables (assuming a reduction of 1.6 years and 3 years for men and women respectively with RA). Costs have been discounted at 6% and life years at 1.5%.

Initial treatment results in one of the eight possible outcomes shown (including therapeutic success, loss of efficacy and death). The outcomes are defined as:

- GI discomfort: moderate to severe dyspepsia, abdominal pain or nausea
- Diarrhoea: severe enough to lead to patient withdrawal from trial
- Symptomatic ulcers: ulcers treated in outpatients setting but sever enough to lead to NSAID discontinuation
- Anaemia: with occult bleeding
- Serious GI events: any GI event resulting in hospitalisation

Patients who achieve therapeutic success on initial therapy remain on that for the remainder of the time in the model. Those who do not find treatment efficacious or have intolerable diarrhoea change immediately to another therapy. The switch is defined according to a set algorithm that depends on the starting NSAID. A reduced version of this algorithm is given in Table 55 was submitted as CiC and has been removed. Patients who experience an adverse GI event have their therapy temporarily withdrawn while the event is treated but are then switched to another therapy.

Table 55: Reduced version of the algorithm for therapy switching

[CiC table removed]

The analysis assumes that all compared therapies are equivalent in terms of efficacy, and rates of cardiovascular events and renal events and so neither cardiovascular nor renal adverse events are considered in the model structure.

The event probabilities for the non-selective NSAID strategy were taken from a variety of sources:

- GI discomfort: Weibull model to provide a GI discomfort probability adjusted for time of drug exposure, based on "pooled analysis of five, 12-week, placebo and active (naproxen) controlled, randomised, parallel group celecoxib clinical trials (Bensen et al, 2000)[93]
- Serious GI events: based on a predictive equation adapted from the Fries risk calculator which uses information from the ARAMIS database – the risk calculator gives the baseline NSAID rate of serious GI events for a population described in terms of age, history of GI events, etc.
- Symptomatic ulcers and anaemia: taken from NSAID only arm of the CLASS trial
- Diarrhoea and lack of efficacy: taken from Edwards et al meta analysis (a commissioned meta-analysis reported in the Pfizer submission)

The relative risks for gastrointestinal events were taken from single sources for the two drugs of interest:

- the SUCCESS trial (study 096) for celecoxib, and
- Edwards et al for valdecoxib.

The Edwards et al analysis was a systematic review commissioned by the manufacturer.

The explanation for the former is that SUCCESS "is the largest study that reports all the inputs to the model at the licensed dose". The source for valdecoxib is stated to be the only source available. Table 56 gives the event probabilities used in the ACCESS model for average risk patients.

Average risk patients were defined as "age 62, no history of GI side effects or complications, no aspirin use and HAQ of 1" (i.e. average age of all patients in SUCCESS). High-risk patients were defined as "age 72, history of GI side effect, aspirin use and HAQ of 2" (i.e. average age of patients over 65 in SUCCESS). Analyses were run separately for men and women, and for OA and RA.

Table 56: Event probabilities and relative risks used in Pfizer model (average risk patients)

	Probability (%) - conventional NSAID	RR - celecoxib	Probability (%) - celecoxib	RR - valdecoxib	Probability (%) - valdecoxib
Loss of efficacy	13.60	1.00	13.60	1.00	13.60
GI discomfort	7.73	0.76	6.23	0.65	5.53
Serious GI event	0.35	0.17	0.06	0.40	0.16
Case fatality of serious GI event	0.05	1.00	0.01	1.00	0.02
Ulcer	0.23	0.47	0.12	0.40	0.10
Anaemia with occult bleeding	0.10	0.67	0.07	0.67*	0.07
Diarrhoea	1.50	1.00	1.50	1.00	1.50

* Assumed to be the same as celecoxib – no data

Resource use information relating to model events was collected by questioning and interviewing physicians who treat OA and RA patients. Unit costs have been taken from routine sources and are expressed in 2002/3 prices.

The base-case results for average risk OA patients are reported in Table 57 and for high risk patients in Table 58.

Table 57: Modelled outcomes – 1000 average risk male OA patients

	NSAID	Celecoxib	Valdecoxib
GI discomfort	82.82	66.76	57.30
Diarrhoea	14.71	14.79	14.83
Ulcers	2.21	1.21	1.03
Anaemia	0.95	0.67	0.67
Serious GI events	3.46	0.76	1.62
Deaths	0.49	0.11	0.23
Life years lost	7.40	1.64	3.47
Total cost per patient	£58,763	£139,741	£133,775

ICER (cox-2 vs NSAID)		£14,049 per life-year gained	£19,115 per life-year gained

Table 58: Modelled outcomes – 1000 high risk male OA patients

	NSAID	Celecoxib	Valdecoxib
GI discomfort	241.55	197.36	170.80
Diarrhoea	14.03	14.27	14.38
Ulcers	5.52	3.18	2.74
Anaemia	2.35	1.73	1.73
Serious GI events	8.91	2.49	4.51
Deaths	1.27	0.35	0.64
Life years lost	12.14	3.40	6.17
Total cost per patient	£104,200	£174,380	£165,102
ICER (COX-2 vs NSAID)		£8,029 per life-year gained	£10,190 per life-year gained

Pfizer believe, from their findings, that celecoxib and valdecoxib represent cost-effective uses of NHS resources. Although valdecoxib and celecoxib were not compared directly there is sufficient detail in their submission to allow an indirect comparison. ICERs for these comparisons are given in the final rows in Table 56, pg 138, and Table 57, pg 138, and show that for both average and high risk patients celecoxib has a higher cost than valdecoxib but is associated with fewer years of life lost. The ICER for changing from valdecoxib to celecoxib is just over £3,000 per life year gained for both average and high risk patients. One way and probabilistic sensitivity analyses were reported. The baseline patient risk had a large impact on the resulting cost-effectiveness and results change considerably with variation in the relative risk of serious GI events for celecoxib (up to £33,000 per life year gained). The results of the probabilistic sensitivity analysis are summarised as follows.

"At a ceiling ratio of £30,000 per life year saved:

- There is a greater than 95% probabilities for both average and high risk patients that celecoxib is cost-effective.
- There is a greater than 95% probability that in the high risk patients valdecoxib is cost-effective.
- There is approximately 90% probability that in the average risk patients valdecoxib is cost-effective."

Although not reported, the assertion is made that the general findings of the sensitivity analyses are similar for valdecoxib.

5.3.2 MSD submission

In this submission rofecoxib or etoricoxib, for patients with either OA or RA, are compared with a range of non-selective NSAID alternatives; rofecoxib and etoricoxib are not compared directly. The alternatives considered are:

- Non-selective NSAIDs alone,
- Non-selective NSAIDs plus PPIs,
- Non-selective NSAIDs plus misoprostol, and
- Non-selective NSAIDs plus H2As.

MSD explore [CiC – text removed], and also all doses up to 50 mg based on clinical trials and meta-analyses . For etoricoxib, a similar approach was desired but because of time constraints their analysis used clinical data for all doses up to 120mg [CiC – text removed].

A decision tree model similar to the published economic analyses of rofecoxib was used (Figure 24). Patients move along the tree from left to right. Model events cover a 1-year time horizon but the calculation of life years gained is undertaken using actuarial life tables (with no differentiation between patients with RA and OA). The cost analysis considered only costs incurred within 1 year and so were not discounted but life years were discounted at a rate of 1.5%.

Events modelled included:

- Major GI events (i.e. PUBs)
- Lower GI events
- Events of sufficient severity to prompt a procedure to exclude a PUB (e.g. endoscopic examination)
- Cardiovascular events

Rofecoxib analyses
Analyses only included data on PUBs that related to occurrences at least 7 days before or after any trial protocol scheduled endoscopic procedure, and were confirmed as clinically significant by an outside expert panel. The rationale for this was to ensure that no protocol driven health care costs were included in the analysis. [CiC – text removed] For the all dose investigation, data were taken from pooled analyses of a larger number of trials, including VIGOR.

The model input probabilities are listed in Table 59 and Table 60, pg 141.

Table 59: Model inputs (probabilities and rates) – Upper GI events

	Non selective NSAID	**Rofecoxib**
CiC removed		
CiC removed	CiC removed	CiC removed
CiC removed	CiC removed	CiC removed
CiC removed	CiC removed	CiC removed
CiC removed	CiC removed	CiC removed
CiC removed	CiC removed	CiC removed
CiC removed	CiC removed	CiC removed
All dose study		
GI adverse events	0.3673	0.3302
PUB rate per 100 patients	0.0313	0.0116
PUB, given GI adverse event	0.0853	0.0351
Suspected PUB (per 100 patient years)	0.0039	0.0009
Suspected PUB, given GI adverse event and not major GI problem	0.0038	0.0009
Treatment given non serious GI adverse event	0.3826	0.2985

Table 60: Model inputs (probabilities and rates) – hospital treatment pathways of PUBs and mortality rate of PUBs

	Base rate	Range
Hospitalisation given PUB	0.207	0.056 to 0.67
Inpatient investigation of suspected PUB	0.25	0.24 to 0.39
Surgery following hospitalisation	0.24	0.09 to 0.39
Death rate given hospitalisation	0.186	Not varied
Death given PUB	0.039	Not varied
Death given clinically diagnosed ulcer	0.036	Not varied

These probability estimates on pathways and mortality are taken from a variety of published sources.

Probability estimates on pathways and mortality are taken from a variety of published sources. In considering treatment options involving non-selective NSAIDs used in combination with prophylactic GPAs MSD assumed no further reduction in upper GI PUBs would be seen from the use of H2As and a 40% reduction in risk of upper GI PUBs was assumed for both misoprostol and PPIs (based on Rostom et al). Estimates of probabilities for cardiovascular events were taken from the Antiplatelet Trialists' Collabration (APTC) endpoints observed in rofecoxib clinical trials. [CiC – text removed]

Resource use information relating to model events was taken from a variety of published and routine data sources. Unit costs have been taken from routine sources and are expressed in 2003 prices. The QALY calculations made use of the Maetzel et al (2001)[282] utility weights. Extensive sensitivity analyses were undertaken, both one-way and probabilistic. A key feature of the SA is that the effect of incorporating lower GI events and CV events was explored.

The base-case results for [CiC – text removed] the all dose investigation are reported in Table 62, pg 142.

Table 61: CiC – table removed.

Table 62: Results – all-dose investigation

	NSAID alone	NSAID + PPI	NSAID + H2A	NSAID + misoprostol	Rofecoxib
Base case analysis					
Total daily cost	£0.40	£1.07	£0.67	£1.03	£0.86
QALYs per 10,000 patients	6683	6745	6683	6745	6776
ICER (rofecoxib vs comparator)	£17,900	(Saving)	£7,159	(Saving)	
Including lower GI effects (from VIGOR)					
Total daily cost	£0.43	£1.09	£0.70	£1.06	£0.87
QALYs per 10,000 patients	6647	6710	6647	6710	6757
ICER (rofecoxib vs comparator)	£14,994	(Saving)	£5,834	(Saving)	
Including CV and lower GI effects					
Total daily cost	£0.63	£1.30	£0.91	£1.26	£1.08
QALYs per 10,000 patients	6261	6324	6261	6324	6406
ICER (rofecoxib vs comparator)	£11,192	(Saving)	£4,324	(Saving)	

MSD believe, from these findings, that rofcoxib is cost-effective in the treatment of OA and RA when compared to non-selective NSAIDs alone or in combination with other therapies. On comparing a non-selective NSAID plus either a PPI or misoprostol, rofecoxib is dominant. The inclusion of CV events leads to an improved cost-effectiveness for rofecoxib [CiC – text removed]. Sensitivity analyses highlight the high degree of sensitivity of results to variation in the risk of PUB and the cost of PPIs.

Etoricoxib analyses

This analysis followed the same approach as the economic evaluation of rofecoxib. Exactly the same model structure was used (see Figure 24). Key differences are the model inputs for upper GI events and drug costs.

Estimates for upper GI events come from a pooled analysis of 10 Phase IIb or Phase III clinical trials that compared etoricoxib with non-selective NSAIDs in OA, RA and ankylosing spondylitis. Probabilities for upper GI events included in the model are listed in Table 63.and pathways for hospital treatment of PUBs including mortality rate are identical to those used in the rofecoxib analysis.

Table 63: Model inputs (probabilities and rates) – Upper GI events

	Non selective NSAID	Etoricoxib
GI adverse events	0.1840	0.1472
PUB rate per 100 patients	0.0294	0.0124
PUB, given GI adverse event	0.1598	0.0842
Suspected PUB (per 100 patient years)	0.0032	0.0022
Suspected PUB, given GI adverse event and not major GI problem	0.0032	0.0024
Treatment given non serious GI adverse event	0.3341	0.2913

Once again, extensive sensitivity analyses were undertaken, both one-way and probabilistic. A key feature of the SA is that the effect of incorporating lower GI events and CV events was explored.

The base-case results are reported in Table 64.

Table 64: Results – base case analysis

	NSAID alone	NSAID + PPI	NSAID + H2A	NSAID + misoprostol	Etoricoxib
Base case analysis					
Total daily cost	£0.37	£1.05	£0.65	£1.01	£0.87
QALYs per 10,000 patients	6705	6769	6705	6769	6802
ICER (etoricoxib vs comparator)	£18,972	(Saving)	£8,534	(Saving)	
Including CV and lower GI effects					
Total daily cost	£0.51	£1.18	£0.78	£1.14	£1.01
QALYs per 10,000 patients	6426	6490	6426	6490	6510
ICER (rofecoxib vs comparator)	£21,727	(Saving)	£9,745	(Saving)	

In line with findings for rofecoxib, MSD believe that etoricoxib is cost-effective in the treatment of OA and RA when compared to non-selective NSAIDs alone or in combination with other therapies. On comparing etoricoxib with a non-selective NSAID plus either a PPI or misoprostol etoricoxib is dominant. Sensitivity analyses again highlight the importance of variations in the risk of PUB and the costs of PPIs.

5.3.3 Boehringer Ingelheim submission

In this submission meloxicam (7.5 mg or 15 mg daily), for patients with OA or RA, is compared with diclofenac retard (100 mg daily) and piroxicam (20 mg daily). An economic evaluation, using a slightly modified version of the Markov model developed by Maetzel, is included. The submission indicates that the model used "has been adapted to a UK health care setting" but full details on the nature of the changes made are not given. It is assumed that COX-2 selective and non-selective NSAIDs do not different in effectiveness but differ in their adverse event profile. Figure 25 shows the model structure; as reported in Maetzel et al, 2002[282] and reproduced by Boehringer. The timeframe for the model is 5 years.

Clinical information concerning the incidence of GI and MI adverse events was based on two trials, MELISSA and SELECT. It was assumed that the relative risk reduction for 15 mg and 7.5 mg of meloxicam was the same, and that "the rate of cardiovascular adverse event was not substantially raised compared to those on standard NSAIDs amongst those on meloxicam 15 mg."

Some of the key clinical assumptions and input parameter values used in the analysis are listed in Table 65, pg 143.

Table 65: Clinical outcome estimates included in model analysis

Variable	Base case value	Source
Dyspepsia requiring medical consultation (%)	10.7	Maetzel (2001)

Hospitalised if complicated UGI event (%)	62.7	Maetzel (2001)
Surgery if hospitalised (%)	8.5	Maetzel (2001)
Mortality in patients with 1st bleed (%)	4.3	Maetzel (2001)
Recurrence of bleed (%)	11.5	Maetzel (2001)
Surgery in patients with 2nd GI bleed (%)	71.1	Maetzel (2001)
Mortality in patient with 2nd bleed (%)	38.7	Maetzel (2001)
% retrying NSAIDs after GI bleed	5.0	Maetzel (2001)
RR increase of clinical UGI event due to prior symptomatic ulcer	2.6	Maetzel (2001)
Mortality after experiencing nonfatal MI (%)	3.5	Maetzel (2001)
Complicated UGI event (3 months) – meloxicam (%)	0.208	MELISSA
Complicated UGI event (3 months) – diclofenac (%)	0.343	MELISSA
Symptomatic ulcer (3 months) – meloxicam (%)	0.139	MELISSA
Symptomatic ulcer (3 months) – diclofenac (%)	0.137	MELISSA
Non fatal MI (3 months) – meloxicam (%)	0.139	MELISSA
Non fatal MI (3 months) – diclofenac (%)	0.274	MELISSA
Complicated UGI event (3 months) – meloxicam (%)	0.372	SELECT
Complicated UGI event (3 months) – piroxicam (%)	0.815	SELECT
Symptomatic ulcer (3 months) – meloxicam (%)	0.149	SELECT
Symptomatic ulcer (3 months) – piroxicam (%)	0.371	SELECT
Non fatal MI (3 months) – meloxicam (%)	0.149	SELECT
Non fatal MI (3 months) – piroxicam (%)	0.074	SELECT

Resource use information relating to model events was taken from a variety of published and routine data sources. Unit costs have been taken from routine sources and are expressed in 2003/04 prices. Costs have been discounted at a rate of 6%. Benefits were discounted at 1.5%. QALY calculations made use of the Maetzel et al (2001) utility weights.

The base case result for an average patient with OA, comparing meloxicam (7.5 mg) against piroxicam (20 mg) is £12,383 per QALY gained. (Note: the precise definition of the 'average patient' is not clear from the submission). When the 15 mg dose is considered, the ICER increases to £23,448 per QALY gained. These estimates are based on the current branded price for meloxicam. When a generic price is used (assumed to be 60% lower price), meloxicam dominates (i.e. lower cost and higher benefits). For patients with a previous history of symptomatic ulcer (without use of PPIs) meloxicam dominates all comparisons made. Reults from extensive one way sensitivity analyses do not change results, in general terms. Unsurprisingly changes in the reduction in the risk of complicated UGI events bring about the largest change in the overall results.

Boehringer conclude that meloxicam (at both 7.5 mg and 15 mg doses) is highly cost effective against diclofenac (100 mg SR) and piroxicam in patients at average risk and more so for patients at high risk of GI events. The patent for meloxicam is due to expire in 2005. In a separate analysis assuming drug prices 60% lower than branded prices an even more favourable result for meloxicam is shown.

5.3.4 Summary

- All three-industry submissions that included a formal economic analysis, used a decision modelling approach. Models vary in some important aspects; for example, whether switching of therapy is considered, timeframe, nature of events considered, and so on. This makes direct comparisons difficult.

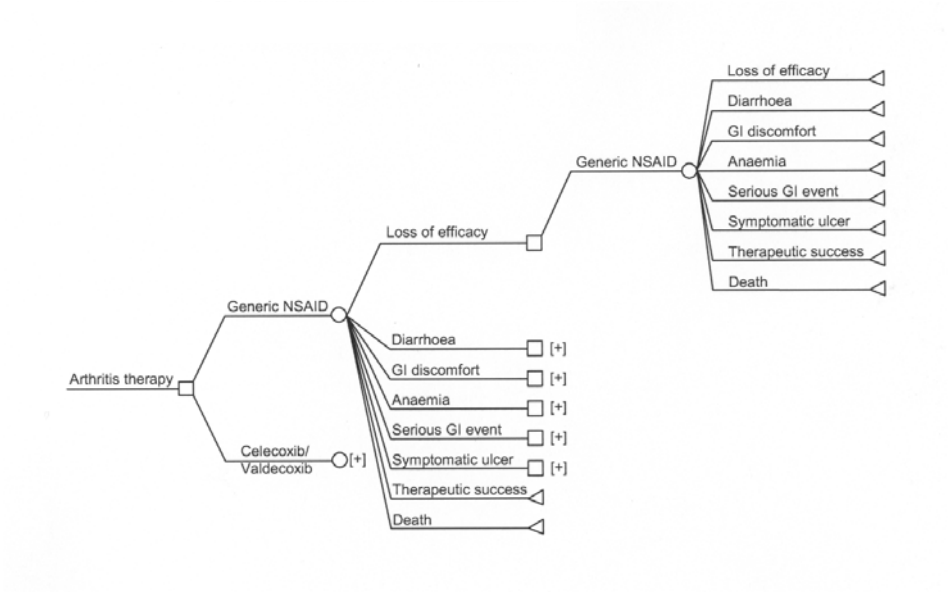
- All analyses compared individual COX-2 selective NSAIDs with a non-selective agent (in some cases with co-therapy). Manufacturer analyses support the widespread use of

celecoxib, rofecoxib, meloxicam, etoricoxib and valdecoxib but none report direct comparisons of COX-2 selective drugs even though this is clearly feasible, especially where manufacturers have more than one product.

- In general terms, the economic analyses presented by the companies are based on clinical estimates derived from single trials, or a small number of trials, rather than a formal systematic review and meta-analysis of the evidence.

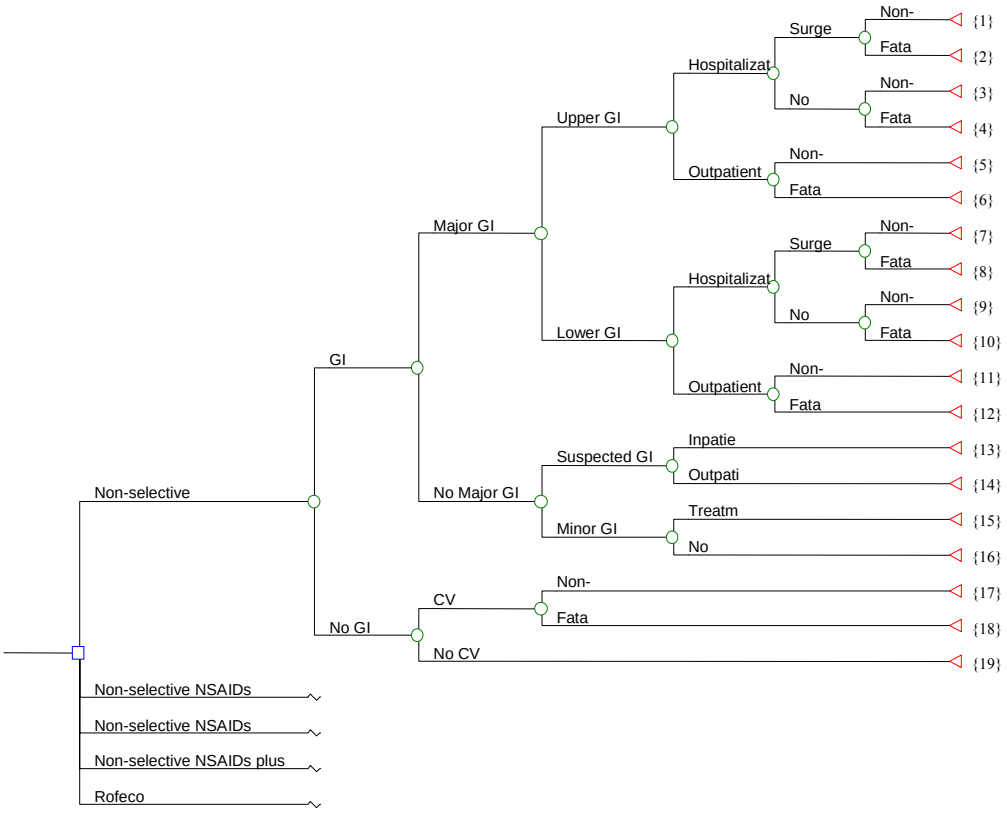
- Sensitivity analyses show, consistently, that cost-effectiveness is more favourable when COX-2 selective NSAIDs are restricted to 'high risk' patients, and when the reduction in the risk of serious GI events is large.

Figure 23: Decision tree used in Pfizer submission



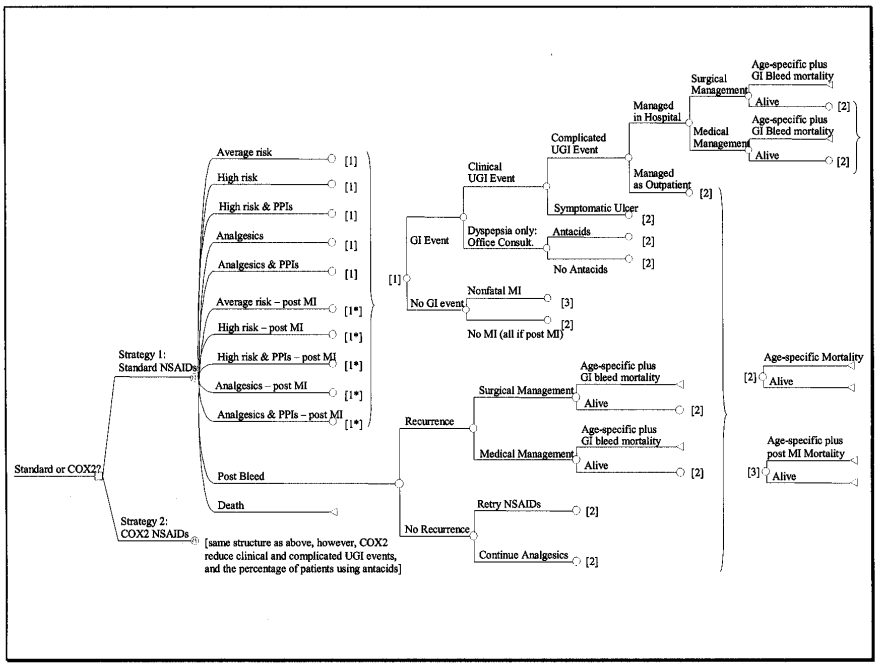
[+] indicates repetition of branch structure

Figure 24: Decision tree used in MSD submission



283 surgery for PUB (nonfatal)
284 surgery for PUB (fatal)
285 inpatient treatment for PUB (nonfatal)
286 inpatient treatment for PUB (fatal)
287 outpatient treatment for PUB (nonfatal)
288 outpatient treatment for PUB (fatal)
289 surgery for lower GI bleed (nonfatal)
290 surgery for lower GI bleed (fatal)
291 inpatient treatment for lower GI bleed (nonfatal)
248 inpatient treatment for lower GI bleed (fatal)
292 outpatient treatment for lower GI bleed (nonfatal)
293 outpatient treatment for lower GI bleed (fatal)
294 inpatient investigation for PUB
295 outpatient investigation for PUB
296 minor GI problem leading to treatment
79 Nonfatal CV Event (APTC endpoint)
297 Fatal CV Event (APTC endpoint)
79,298 no additional resource use

Figure 25: Markov model used in Boehringer Ingelheim submission (diagram of Maetzel model)



Repetitive subtrees [1] and [2] are represented once.
PPI: Proton Pump Inhibitor; MI: myocardial infarctions; GI: gastrointestinal
*: patients in post MI states will go through subtree 1 without further MIs

5.4 The Assessment Group Model (AGM)

The Assessment Group has undertaken a new modelling exercise that used the Markov model developed originally by Maetzel et al (2001)[282] as a starting point (see section 5.2 for a discussion of the published Maetzel model) and built on it in a number of ways, including: (1) introducing an initial cycle where drug switching could take place, (2) revising the model input parameters, (3) using the revised model to consider all COX-2 drugs (for which adequate data were available), and (4) undertaking probabilistic sensitivity analyses (to be included as an addendum to this report). The methods and results of this modelling work are reported in this section.

The Assessment Group Model (AGM) is a Markov model with a time cycle of 3 months, and runs by default for a time horizon of 5 years. The model was constructed using TreeAge DATA Pro.

The model has been designed to run in two different forms: the 'full AGM', which includes an initial drug switching cycle, and the 'simpler AGM', where there is no initial cycle and no opportunity for the patient to switch NSAID.

The full AGM, in our view, has the more appropriate model structure for two reasons: first, it directly address the policy question at hand, and second, it models strategies that are in line with current NSAID-prescribing practice. That is, the full AGM allows for the possibility that patients will, in the short-term, switch from an initial NSAID therapy to an alternative.

However, this section of the report initially describes the methods and results for the simpler AGM (with no initial switching cycle). The reason for this is that the simpler model is more directly comparable with previous modelling work and the results can more easily be compared with the results of the company analyses. In broad terms, the results of the simpler version of our model and the fuller model are not very different.

Both versions of the AGM are designed to compare COX-2 selective NSAIDs individually with non-selective NSAIDs, not to compare non-selective NSAIDs with each other. Therefore, cost-effectiveness results have been obtained for each COX-2, compared to a non-selective NSAID, initially for a general population with no special risk factors but additionally for other patient populations with defined risk factors (e.g. previous GI event, etc.).

5.4.1 The simpler AGM: methods

A simulated patient initially starts in the model on one NSAID (either a non-selective or a COX-2 selective NSAIDs). Patients then immediately enter a recurring process (i.e. the Markov model) in which they are at risk of GI and MI events. There is no provision for switching NSAIDs. As time goes on, for each simulated patient, the NSAID they are receiving may be withdrawn and/or PPI may be added. Mortality from MI and GI complications is taken into account, as well as mortality from other causes.

5.4.2 Markov states and cycles

On entry into the model a patient is in one of the Markov model states. The majority of states are defined by four characteristics (i.e. NSAID use, PPI use, post GI or not, and post MI or not), as shown in Table 66. For example, a simulated patient might be taking the NSAID with no PPI, having experienced neither a GI nor an MI event. There are also (immediate) Post Bleed states (with or without Post MI) and Death.

Table 66: Markov states in the Assessment Group Model

NSAID use	PPI	Post GI	Post MI
yes	no	no	no
no	yes	yes	yes

NSAIDs may be taken with or without PPI. Patients who have had a previous serious UGI event are in "Post GI" states, while patients with a previous MI are in "Post MI" states. For non-selective NSAIDs, the combination "No PPI" with "Post GI" is not permitted.

Patients may be in the "Post GI" states as a result of starting in the model having never previously had a GI event but transitions within the model mean that a GI event is experienced. Alternatively, patients may be in the "Post GI" states simply because the model is being run for a high risk cohort of patients with previous UGI history, in which case only the "Post GI" states will be used.

We have maintained the assumption in the Maetzel model that only one new event (GI or MI) can occur in any 3-month cycle. We have also maintained the assumption that second MIs are fatal; we appreciate that this is not usual. The possibility that the first MI can be fatal is incorporated in the standard mortality tables; and additional probability of death from MI is added in the "Post MI" states.

Figure 26 shows possible outcomes following a GI event in a Markov cycle in the model. Patients move from left to right through the tree and circles indicate chance nodes. The label below each branch in the figure indicates the probability of a patient following that branch, conditional on them reaching the previous chance node. If there is no GI event in a Markov cycle, the possibilities are shown in Figure 27. An exception here is that non-fatal MI is omitted in "Post MI" states as we assume a second MI would be fatal. The Markov state reached at the end of the cycle is shown in

Table 67.

Data inputs to the Markov cycles consist of probabilities of any GI event, clinical GI event, complicated GI event, and non-fatal MI. Baseline risks are given for non-selective NSAIDs, with relative risks for adding PPI, for COX-2 selective NSAIDs (assumed relative to ibuprofen), and for previous UGI event.

Figure 26: Handling GI events

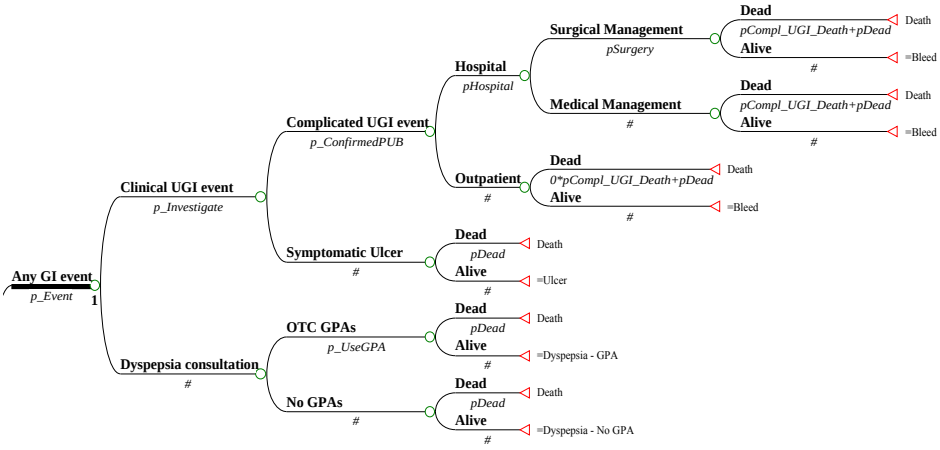


Figure 27: Other events

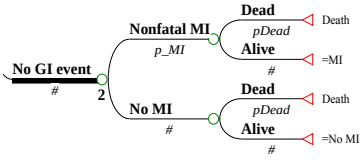


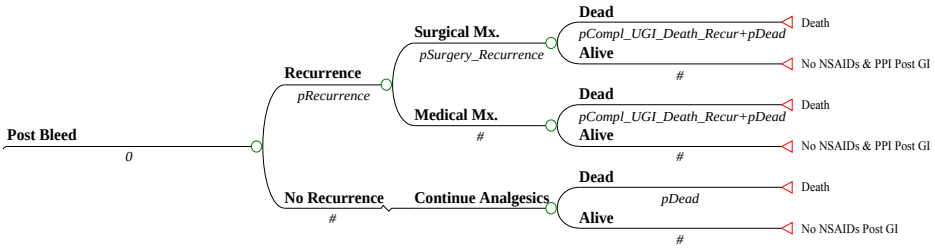
Table 67: Markov transitions

Event occurring during cycle	Markov state at end of cycle
Death (any cause)	Death
Complicated UGI event (Bleed)	Post Bleed ("Post MI" as at start)
Other clinical UGI event (Ulcer)	Add PPI and "Post GI" to starting state
Dyspepsia – GPA used	Add PPI to starting state
Dyspepsia – GPA not used	Same as at start of cycle
MI	Add "Post MI" to starting state
No event (No MI)	Same as at start of cycle

Consider, for example, a patient in state "NSAID & PPI" at the start of the Markov cycle. If this patient developed an ulcer during the Markov cycle the patient then moves into the state "NSAID & PPI, Post GI".

The only states remaining to be described are the "Post Bleed" states. The structure for these is shown in Figure 28, pg 152. For a patient who has had an MI and now experiences a bleed (i.e. "Post Bleed & Post MI"), the possible transitions are to equivalent "Post MI" to those shown in Figure 28. In our version of the model (unlike the original Maetzel model), all "Post Bleed" transitions are to "No NSAID" states, and thus no further NSAID will be taken after a bleed. The original Maetzel model allows a small probability of re-trying NSAIDs after a bleed with no recurrence. To include this possibility in a model allowing switching of NSAIDs would require separate "Post Bleed" states and thus further complicate the model. Our justification for omitting this possibility is also based on the fact that Maetzel reported a sensitivity analysis on the probability of re-trying, which shows that it makes very little difference to the results to the model.

Figure 28: Post-Bleed transitions



5.4.3 Costs

Costs in the model consist of costs of medication (i.e. NSAIDs, analgesics and PPIs), and costs of managing events as they occur. Table 68 shows the costs in the model:

Table 68: Costs included in the AGM

Item	per	Value (£)	Source
Ibuprofen	Day	0.11	BNF
Diclofenac	Day	0.13	BNF
Celecoxib	Day	0.718 (OA)	BNF

		1.436 (RA)	
Etodolac	Day	0.52	BNF
Etoricoxib	Day	0.82	BNF
Meloxicam	Day	0.33 (OA) 0.46 (RA)	BNF
Rofecoxib	Day	0.77	BNF
Valdecoxib	Day	0.77	BNF
PPI	Day	0.46	BNF
Analgesics	Day	0.05	BNF
Surgical treatment of PUB	Case	3258	BI
Medical treatment of PUB	Case	445	BI
Outpatient treatment of PUB	Case	308	BI
Endoscopy for ulcer	Case	337	BI
Dyspepsia consultation	3 mo	28.52	BI
Dyspepsia treatment (H2RA)	Day	0.09	BNF
Non-fatal MI	Case	1383	BI
Bleed follow-up consultation	3 mo	87	BI
Post-MI management	3 mo	114	BI

BI = Company submission (Boehringer Ingelheim), BNF = British National Formulary

5.4.4 Utilities

We have maintained the utility structure from the Maetzel model. The utilities actually used are shown in Table 69. They represent the (undiscounted) QALYs accruing over one 3-month cycle in which the given event occurs. Note that 0 QALYs are scored if death occurs during the cycle. This may appear unreasonable for "other causes" death but the difference is likely to be small, and to cancel out between different arms of the model.

Table 69: Utilities (expressed as QALYs over 3 months) in the model

Event	QALYs per 3-month cycle
Arthritis	0.172
Dyspepsia	0.126
Endoscopy (no ulcer)	0.115
Endoscopy (ulcer)	0.095
MI	0
PUB (Medical management)	0.078
PUB (Outpatient treatment)	0.095
PUB (Surgery)	0
Post-MI states	Multiply by 0.97

The probabilities for the later Markov cycles are calculated from the data in Table 70. Details of the methods used are in Appendix 9. Here, absolute risks are given for ibuprofen and diclofenac, and relative risks for COX-2 selective NSAIDs, compared to ibuprofen.

Table 70: Data for main Markov cycles

	Absolute or relative risk (RR)	Source & Comment
Risk of any GI event		
Ibuprofen	31.15 per 100 person yrs	CLASS[159]+.
Diclofenac	37.21 per 100 person yrs	CLASS[159]+

	Absolute or relative risk (RR)	Source & Comment
Celecoxib	RR 0.95 (95%CI 0.76 to 1.21)	Assessment group meta-analysis
Etodolac	RR 0.85 (0.72 to 1.01)	Assessment group meta-analysis
Etoricoxib	RR 0.45 (0.22 to 0.92)	Assessment group meta-analysis
Meloxicam	RR 0.72 (0.52 to 1.07)	Assessment group meta-analysis
Rofecoxib	RR 0.84 (0.45 to 1.60)	Assessment group meta-analysis
Valdecoxib	RR 0.64 (0.52 to 0.78)	Assessment group meta-analysis
No NSAID	RR 0.45	Assumed equivalent to lowest COX-2
Adding PPI	RR 0.40 (0.32 to 0.51)	Rostom et al[126] & Ekstrom et al[30]
Risk of clinical GI event (PUB)		
Ibuprofen	3.2 per 100 person yrs	CLASS[159]+
Diclofenac	1.19 per 100 person yrs	CLASS[159]+
Celecoxib	RR 0.64 (95% CI 0.46 to 0.89)	Assessment group meta-analysis.
Etodolac	RR 0.32 (0.15 to 0.71)	Assessment group meta-analysis
Etoricoxib	RR 0.23 (0.05 to 1.08)	Assessment group meta-analysis
Meloxicam	RR 0.57 (0.30 to 1.08)	Assessment group meta-analysis
Rofecoxib	RR 0.43 (0.32 to 0.57)	Assessment group meta-analysis
Valdecoxib	RR 0.12 (0.03 to 0.59)	Assessment group meta-analysis
No NSAID	RR 0.23	Assumed equivalent to lowest COX-2
Adding PPI	RR 0.4 (CI 0.32 to 0.51)	Rostom et al[126] & Ekstrom et al[299]
Risk of complicated GI event (POB)		
Ibuprofen	1.14 per 100 person yrs	CLASS[159]+
Diclofenac	0.48 per 100 person yrs	CLASS[159]+
Celecoxib	RR 0.57 (0.34 to 0.97)	Assessment group meta-analysis
Etodolac	RR 0.39 (0.12 to 1.24)	Assessment group meta-analysis
Etoricoxib	RR 0.46 (0.07 to 3.10)	Assessment group meta-analysis
Meloxicam	RR 0.52 (0.26 to 1.05)	Assessment group meta-analysis
Rofecoxib	RR 0.40 (0.23 to 0.70)	Assessment group meta-analysis
Valdecoxib	RR 0.38 (0.17 to 0.86)	Assessment group meta-analysis
No NSAID	RR 0.38	Assumed equivalent to lowest COX-2
Adding PPI	RR 0.4 (CI 0.32 to 0.51)	Rostom et al[126]& Ekstrom et al[299]
Risk of MI		
Ibuprofen	0.24/100 person years	CLASS[159]
Diclofenac	0.23/100 person years	CLASS[159]
Celecoxib	RR 1.87 (95% CI 1.06 to 3.30)	Assessment group meta-analysis
Etodolac	RR 1.87 (95% CI 1.06 to 3.30)	Assumed same as celecoxib
Etoricoxib	RR 1.58 (0.06 to 38.66)	One trial only (Matsumoto 2002[251], vs naproxen)
Meloxicam	RR 1.87 (95% CI 1.06 to 3.30)	Assumed same as celecoxib
Rofecoxib	RR 2.92 (1.29 to 6.60)	Assessment group meta-analysis
Valdecoxib	RR 0.23 (0.06 to 0.90)	Assessment group meta-analysis
No NSAID	0.37/100 person years	See note below
Adding PPI	RR 1	Assumed PPI does not affect MI rates

+: non-aspirin users; ++: This figure comes from Rostom review and is for ENDOSCOPIC gastric ulcers.

Note: Effective antiplatelet therapy with aspirin reduces the risk of MI in low risk patients by about a third (risk reduction 30%; 95% CI 21% to 38%)[300]. Naproxen may provide a similar level of benefit and in a recent case controlled study ibuprofen had a protective effect similar to naproxen.[301] We have assumed that ibuprofen and diclofenac may have a similar beneficial effect on MI rate but we have explored the possibility that non-selective NSAIDs have no effect at all on MI rates.

Other model parameters are shown in Table 71.

Table 71: Other model parameters

Parameter	Value	Source
RR of GI events for patients with previous GI history	2.6	Maetzel model[282]
Hospitalisation given complicated GI event	0.432	CLASS[159]: see below
Surgery given hopitalisation	0.085	Maetzel model[282]: see below
Death given complicated GI event	0.03	VIGOR[209], CLASS[371}, MUCOSA[302]: see below
Recurrence of GI bleed	0.1145	Maetzel model[282]
Surgery given recurrence of GI bleed	0.7113	Maetzel model[282]
Extra mortality risk post MI	3.5/1000 years	Maetzel model[282]

GI events and previous GI history
The parameter "RR of GI events for patients with previous GI history" is applied for risks of clinical and complicated GI events (PUBs and POBs) to patients in all "Post GI" states in the model. Note that in the model structure described above, patients who have had a bleed during the model are in a "No NSAID Post GI" state. However, as a result of the new initial 3-month cycle in the AGM model (in contrast to the original Maetzel model), we have some "No NSAID" states which are not "Post GI".

The risk of serious GI events needs to recognise the difference between "No NSAID Post GI" states and "No NSAID" states (which are not "Post GI") [303] For the "No NSAID" states (which are not "Post GI"), we have assumed that the risk of GI events is equivalent to the best COX-2 selective NSAID. For the "No NSAID Post GI" states, we have again assumed that the risk of GI events is equivalent to the best COX-2 selective NSAID but have applied the additional previous GI history risk.

Maetzel assumes that the risk for "No NSAIDs Post GI" is the same as the risk for COX-2 selective NSAIDs without the additional "Post GI" risk.[303]

Hospitalisation
Maetzel in the CCOHTA report quotes a figure of 62.7% for hospitalisation of patients with a complicated UGI event, based on the MUCOSA study of RA patients. Since RA patients are likely to be sicker and MUCOSA was published in 1995, we studied clinical cases where complicated upper GI events occurred in the CLASS study. Of the 44 patients with clinically significant UGI events reported in detail on the FDA website, 19 patients, of 44 (43.2%), were admitted to hospital (in one case the patient was 'had a prolonged emergency room stay and intravenous hydration' – it was assumed that such a patient would be hospitalised in the UK). Five (26.3%) of the 19 hospitalised patients in CLASS had surgery: two for perforations. There were no UGI related deaths in CLASS. Of the 44 case reports on the FDA website 9 (20.5%) patients had blood transfusions.

Surgery
Maetzel quotes a baseline rate for surgery of 8.5% (CI 4.8% to 12.2%) for hospitalised patients. We have not identified any better estimates for this parameter and have accepted this baseline figure and a range of 3.3% to 35.7% quoted by Maetzel.

Mortality
In the VIGOR study 53 complicated PUBs were reported and 4 deaths (7.5%), directly due to upper GI events, occurred: one in the naproxen group and 3 for rofecoxib. In MUCOSA 1 patient of 67 definite UGI complications died. Combining data on deaths from MUCOSA,

VIGOR and CLASS indicates that 3.0% of people with a complicated UGI died (assuming 39 events in CLASS). This figure is close to that used by Maetzel who quotes a figure of 4.3% from data recorded before 1986.[304]

5.5 Results for the simpler AGM

5.5.1 Results for the average patient

The model was initially run for a cohort of standard patients with starting age 58. Comparisons against ibuprofen (without PPI) are shown in Table 72 and against diclofenac (without PPI) alone in Table 73.

Table 72: Results comparing single COX-2 selective NSAIDs against ibuprofen

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
Ibuprofen	£510.00		3.19151		
Celecoxib (OA)+	£1,462.39	£942.38	3.19454	0.00303	£311,000
Celecoxib (RA)+	£2,570.14	£2,050.13	3.19454	0.00303	£677,000
Etodolac	£1,144.80	£624.79	3.2016	0.01009	£61,900
Etoricoxib	£1,515.63	£995.62	3.2206	0.02909	£34,200
Meloxicam (OA)+	£855.02	£335.01	3.20645	0.01494	£22,400
Meloxicam (RA)+	£1,055.81	£535.80	3.20645	0.01494	£35,900
Rofecoxib	£1,559.56	£1,039.55	3.19805	0.00654	£159,000
Valdecoxib	£1,466.42	£946.41	3.21817	0.02666	£35,500

All incremental analysis is compared to ibuprofen. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY). +:Licensed doses differences for OA and RA associated with different costs.

Table 73: Results comparing single COX-2 selective NSAIDs against diclofenac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
Diclofenac	£518.86		3.1875		
Celecoxib (OA)+	£1,462.39	£931.70	3.19454	0.00704	£132,000
Celecoxib (RA)+	£2,570.14	£2,039.45	3.19454	0.00303	£673,000
Etodolac	£1,144.80	£614.11	3.2016	0.0141	£43,600
Etoricoxib	£1,515.63	£984.94	3.2206	0.0331	£29,800
Meloxicam (OA)+	£855.02	£324.33	3.20645	0.01895	£17,100
Meloxicam (RA)+	£1,055.81	£525.12	3.20645	0.01895	£27,700
Rofecoxib	£1,559.56	£1,028.87	3.19805	0.01055	£97,500
Valdecoxib	£1,466.42	£935.73	3.21817	0.03067	£30,500

All incremental analysis is compared to diclofenac. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY). +:Licensed doses differences for OA and RA associated with different costs.

For both ibuprofen and diclofenac as comparators, all of the COX-2 products are associated with higher costs (i.e. positive incremental costs) and small increases in effectiveness (i.e. positive incremental effectiveness), measured in terms of QALYs. The magnitude of the incremental costs and the incremental effects, and therefore the ICERs, vary considerably across all COX-2 drugs.

In order to explore the sensitivity of our results to variation in the comparator we also compared COX-2 seletive NSAIDs against non-selective NSAIDs with PPI. The results are

shown in Table 74 and Table 75. In most cases, non-selective NSAID plus PPI dominates the COX-2 selective NSAIDs (i.e. the COX-2 is associated with both a higher cost and poorer effectiveness). This is because in this model the relative risk of GI events for adding PPI to a non-selective NSAID is lower (more favourable) than the relative risk for COX-2 selective NSAIDs compared to non-selective NSAIDs. In a few cases, the COX-2 selective NSAID is more effective than non-selective NSAID plus PPI, but with a high incremental cost-effectiveness ratio. Finally, in the case of meloxicam for OA, the COX-2 selective NSAID is cheaper, but less effective, than non-selective NSAID plus PPI. In this case, we have printed the ICER in *italics*: a low ICER favours non-selective NSAID plus PPI.

Table 74: Results comparing single COX-2 selective NSAIDs against ibuprofen plus PPI

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
Ibuprofen+PPI	£950.35		3.22033		
Celecoxib (OA)+	£1,462.39	£512.04	3.19454	-0.02579	D
Celecoxib (RA)+	£2,570.14	£1,619.79	3.19454	-0.02579	D
Etodolac	£1,144.80	£194.45	3.2016	-0.01873	D
Etoricoxib	£1,515.63	£565.28	3.2206	0.00027	£2,100,000
Meloxicam (OA)+	£855.02	-£95.33	3.20645	-0.01388	*£6,870*
Meloxicam (RA)+	£1,055.81	£105.46	3.20645	-0.01388	D
Rofecoxib	£1,559.56	£609.21	3.19805	-0.02228	D
Valdecoxib	£1,466.42	£516.07	3.21817	-0.00216	D

All incremental analysis is compared to ibuprofen. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY). ICER in *italics* means both incremental values are negative. D means COX-2 selective NSAID is dominated by ibuprofen plus PPI. +:Licensed doses differences for OA and RA associated with different costs.

Table 75: Results comparing single COX-2 selective NSAIDs against diclofenac plus PPI

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
Diclofenac+PPI	£970.55		3.21803		
Celecoxib (OA)+	£1,462.39	£491.84	3.19454	-0.02349	D
Celecoxib (RA)+	£2,570.14	£1,599.59	3.19454	-0.02349	D
Etodolac	£1,144.80	£174.25	3.2016	-0.01643	D
Etoricoxib	£1,515.63	£545.08	3.2206	0.00257	£212,000
Meloxicam (OA)+	£855.02	-£115.53	3.20645	-0.01158	*£9,980*
Meloxicam (RA)+	£1,055.81	£85.26	3.20645	-0.01158	D
Rofecoxib	£1,559.56	£589.01	3.19805	-0.01998	D
Valdecoxib	£1,466.42	£495.87	3.21817	0.00014	£3,500,000

All incremental analysis is compared to diclofenac. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY). ICER in *italics* means both incremental values are negative. D means COX-2 selective NSAID is dominated by diclofenac plus PPI. +:Licensed doses differences for OA and RA associated with different costs.

5.5.2 Results for high risk patients

We also ran this model for patients with previous history of GI events. In this case, it would be standard practice to compare COX-2 selective NSAID alone against non-selective NSAID plus PPI. The results are shown in Table 76 and Table 77.

Table 76: Results comparing single COX-2 selective NSAIDs against ibuprofen plus PPI for patients with previous history of GI events

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
Ibuprofen+PPI	£980.50		3.21381		
Celecoxib (OA)	£1,464.91	£484.41	3.18653	-0.02728	D
Celecoxib (RA)	£2,545.18	£1,564.68	3.18653	-0.02728	D
Etodolac	£1,141.45	£160.95	3.19667	-0.01714	D
Etoricoxib	£1,496.87	£516.37	3.2151	0.00129	£400,000
Meloxicam (OA)	£869.22	-£111.28	3.19908	-0.01473	*£7,550*
Meloxicam (RA)	£1,065.37	£84.87	3.19908	-0.01473	D
Rofecoxib	£1,544.82	£564.32	3.19248	-0.02133	D
Valdecoxib	£1,461.80	£481.30	3.2146	0.00079	£609,000

All incremental analysis is compared to ibuprofen. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY). ICER in *italics* means both incremental values are negative. D means COX-2 selective NSAID is dominated by ibuprofen plus PPI.

Table 77: Results comparing single COX-2 selective NSAIDs against diclofenac plus PPI for patients with previous history of GI events

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
Diclofenac+PPI	£982.23		3.21538		
Celecoxib (OA)	£1,464.91	£482.68	3.18653	-0.02885	D
Celecoxib (RA)	£2,545.18	£1,562.95	3.18653	-0.02885	D
Etodolac	£1,141.45	£159.22	3.19667	-0.01871	D
Etoricoxib	£1,496.87	£514.64	3.2151	-0.00028	D
Meloxicam (OA)	£869.22	-£113.01	3.19908	-0.0163	*£6,930*
Meloxicam (RA)	£1,065.37	£83.14	3.19908	-0.0163	D
Rofecoxib	£1,544.82	£562.59	3.19248	-0.0229	D
Valdecoxib	£1,461.80	£479.57	3.2146	-0.00078	D

All incremental analysis is compared to diclofenac. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY). ICER in *italics* means both incremental values are negative. D means COX-2 selective NSAID is dominated by diclofenac plus PPI.

The results show a very similar pattern to those reported in Table 74 and Table 75, with the COX-2 drugs again looking generally unattractive from a cost-effectiveness point of view.

5.5.3 The full AGM: methods

In the full version of the model a simulated patient initially starts in the model on one NSAID (either a non-selective or a COX-2 selective NSAID). If this is acceptable then they continue on that NSAID at least until the end of the first 3-month cycle. However, if the NSAID is unacceptable (for whatever reason), they will switch early (i.e. within the first 3 months) to a different NSAID. Patients then enter a recurring process (i.e. the Markov model proper) in which they are at risk of GI and MI events. From this point on the process of the Markov model and the data used to populate the model is exactly as described above for the simpler AGM. Separate Markov states are used for patients on different NSAIDs.

Even in the full AGM there is no provision for switching NSAIDs after the initial cycle (for simplicity of modelling). The purpose of the model is still to enable assessment of each COX-2 selective NSAID individually, not to compare non-selective NSAIDs with each other. Accordingly, a fixed pattern of non-selective NSAIDs is used as the basis for comparison, and only one COX-2 selective NSAID is considered in the model at any one time. Ibuprofen and diclofenac are the only two non-selective NSAIDs available for use in the model. These were

selected on the basis of current patterns of NSAID use in England and Wales. Three possible general strategies of NSAID use are compared (shown in Table 78).

Table 78: Strategies compared in the AGM

Strategy	First line treatment (N1)	Second line treatment (N2)
No COX-2	ibuprofen	diclofenac
COX-2 second	ibuprofen	COX-2 selective NSAID
COX-2 first	COX-2 selective NSAID	ibuprofen

Therefore, for the strategy described as 'No COX-2' this always refers to initial treatment with ibuprofen and, if within the first 3 months ibuprofen is judged not to be acceptable for whatever reason, a switch to diclofenac may happen. Similarly, the strategy defined as 'COX-2 second' always indicates that patients initially receive ibuprofen but may switch to a COX-2 selective NSAID within the first 3 months if ibuprofen is not acceptable.

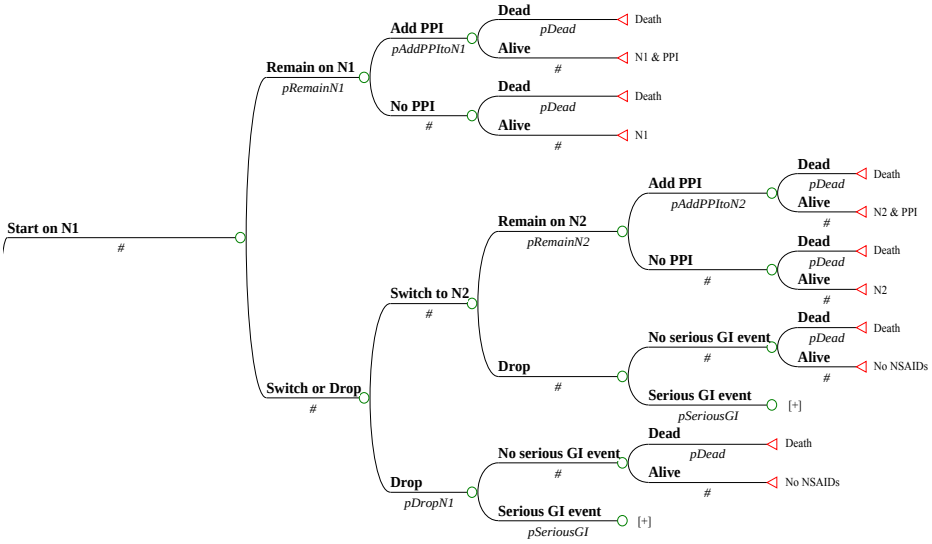
5.5.4 Initial model cycle (i.e. the first 3 months)

The basic structure for the initial sequences for patients with no special risk factors is shown in Figure 29. The probabilities on the branches in this initial cycle of the model are calculated from data given by Langman and colleagues who describe NSAID switching patterns in primary care in the UK.[75] Although the patterns described by Langman are not specifically those of patients with OA and RA, we believe that the patterns are sufficiently representative of people with these conditions in the community. Details of the calculations are shown in Appendix 8.

For the purpose of costing, switching from N1 to N2 (or dropping N1) is assumed to take place on average after 30 days, and dropping N2 after a further 30 days. If PPI is added to an existing NSAID, it is assumed to be added on average half way through the remaining part of the cycle.

When modelling a patient population with a previous history of UGI events (i.e. one the high risk subgroups), the tree is simplified in that it is assumed that such patients would never be given a non-selective NSAID without a PPI. The follow-up to serious GI events in this initial treatment phase is the same as that for later Markov cycles, described below.

Figure 29: The initial cycle



5.5.5 Transition Probabilities and Rates

The transition probabilities for the initial cycle are shown in Table 79 (and see Appendix 8 for further details). The probability of switching to a different NSAID is deduced since the probabilities for four outcomes must add to 1. Note that actual probabilities are given for ibuprofen and diclofenac, but probabilities for COX-2 selective NSAIDs are given relative to ibuprofen.

Table 79: Data for initial cycle

Drug	Probability or RR	Source & Comment
Probability of taking no further NSAIDs in the first 3 months after prescription		
Ibuprofen	0.315	Langman et al.
Diclofenac	0.265	Langman et al.
Celecoxib	RR 1	Assumed same as ibuprofen
Etodolac	RR 1	Assumed same as ibuprofen
Etoricoxib	RR 1.072	Hunt et al, 6 week trial
Meloxicam	RR 1	Assumed same as ibuprofen
Rofecoxib	RR 0.757	Range of RR 0.55 to 1.041. Mean value for rofecoxib doses 12.5 to 25 mg
Valdecoxib	RR 1	Assumed same as ibuprofen
Probability of remaining on the same drug (alone)		
Ibuprofen	0.514	Langman et al.
Diclofenac	0.603	Langman et al.
Celecoxib	RR 1	Assumed same as ibuprofen
Etodolac	RR 1	Assumed same as ibuprofen
Etoricoxib	RR 0.992	Hunt et al, 6 week trial
Meloxicam	RR 1	Assumed same as ibuprofen
Rofecoxib	RR 1.034	Mean value for rofecoxib doses 12.5 to 25 mg

Valdecoxib	RR 1	Assumed same as ibuprofen
Probability of adding PPI to given NSAID		
Ibuprofen	0.026	Langman et al
Diclofenac	0.036	Langman et al.
Celecoxib	RR 1	Assumed same as ibuprofen
Etodolac	RR 1	Assumed same as ibuprofen
Etoricoxib	RR 1	Assumed same as ibuprofen
Meloxicam	RR 1	Assumed same as ibuprofen
Rofecoxib	RR 1	Assumed same as ibuprofen
Valdecoxib	RR 1	Assumed same as ibuprofen

In all cases, RR refers to comparison with ibuprofen.

5.6 Results for the full AGM

5.6.1 Results for the average patient

The full model was initially run for a cohort of standard patients with starting age 58. The results are as in Table 80. As before, separate results for OA and RA are given for celecoxib and meloxicam.

Table 80: Base case results

Celecoxib (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£511.96	£70.72	3.20354	-0.00074	(Dominated)
COX-2 First	£955.48	£514.24	3.20498	0.00071	£726,000

ICER for "COX-2 First" relative to "No COX-2"

Celecoxib (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£598.63	£157.39	3.20354	-0.00074	(Dominated)
COX-2 First	£1,564.54	£1,123.30	3.20498	0.00071	£1,590,000

ICER for "COX-2 First" relative to "No COX-2"

Etodolac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£486.40	£45.16	3.20425	-0.00003	(Dominated)
COX-2 First	£780.19	£338.95	3.20882	0.00454	£74,600

ICER for "COX-2 First" relative to "No COX-2"

Etoricoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£515.46	£74.21	3.20566	0.00138	£53,600
COX-2 First	£983.61	£468.15	3.21872	0.01306	£35,800

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£441.25		3.20428		
COX-2 First	£983.61	£542.36	3.21872	0.01444	£37,600

Meloxicam (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£464.31	£23.06	3.20446	0.00018	£126,000
COX-2 First	£621.67	£157.36	3.21106	0.00661	£23,800
Excluding the option "COX-2 Second" (by extended dominance):					
No COX-2	£441.25		3.20428		
COX-2 First	£621.67	£180.43	3.21106	0.00679	£26,600

Meloxicam (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£480.01	£38.77	3.20446	0.00018	£212,000
COX-2 First	£732.05	£252.04	3.21106	0.00661	£38,200
Excluding the option "COX-2 Second (by extended dominance):					
No COX-2	£441.25		3.20428		
COX-2 First	£732.05	£290.81	3.21106	0.00679	£42,800

Rofecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£521.90	£80.65	3.2039	-0.00038	(Dominated)
COX-2 First	£1,034.94	£593.69	3.20592	0.00165	£361,000

ICER for "COX-2 First" relative to "No COX-2"

Valdecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£511.56	£70.32	3.20556	0.00128	£54,900
COX-2 First	£959.91	£448.35	3.21728	0.01173	£38,200
Excluding the option "COX-2 Second (by extended dominance):					
No COX-2	£441.25		3.20428		
COX-2 First	£959.91	£518.66	3.21728	0.01301	£39,900

Except where otherwise stated, ICER for each option is relative to the previous option listed. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY).

These results are broadly consistent with those reported in Table 72 and Table 73 for the analyses using the simpler AGM. If we look first at the results relating to celecoxib, they indicate that its use second line (after initially trying ibuprofen) is dominated by the 'No COX-2' strategy (i.e. ibuprofen followed by diclofenac, if required) – it is associated with both a higher cost and a poorer level of effectiveness. The use of celecoxib first line is more promising in that the incremental effect is positive (albeit very small) but the cost increase is considerable giving ICERs in excess of £700,000 per QALY gained. The COX-2 drugs that have ICERs relating to first line use that are below £50,000 per QALY are etoricoxib, meloxicam, and valdecoxib. A strategy of second line use of COX-2 drugs looks very unattractive from a cost-effectiveness point of view for all of the drugs considered here.

5.6.2 Sensitivity Analysis

We have conducted a number of univariate sensitivity analyses where the sensitivity of the results of the full AGM are explored. The parameters varied are the relative risks of GI events and the risk of MI.

Varying relative risks of GI events

For this analysis, we set the relative risks of GI events to the lower and upper 95% confidence limits shown in Table 70. For each COX-2 selective NSAID, we set the risks of any GI event, clinical GI event, and complicated GI event simultaneously to low values and then to high values. To maintain our assumption that risks for "No NSAID" were equivalent to the lowest COX-2, we have changed the risks for "No NSAID" in line with the other changes. Thus, the costs and effects for the comparator strategy of "No COX-2" alter, even though this is a sensitivity analysis about relative risks of COX-2 selective NSAIDs compared to ibuprofen. The results for all of the COX-2 drugs considered here are shown in Appendix 10. By way of illustration the results from using the lower values for Etodolac are shown in Table 81, while the results from the higher values for the same drug are in Table 82. In general terms, the results are highly sensitive to variation in the value of the relative risk of GI events.

Table 81: Results with relative risk for all types of GI event at the lower confidence limits (favouring COX-2 selective NSAIDs)

Etodolac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£408.12		3.20925		
COX-2 Second	£450.29	£42.17	3.21132	0.00207	£20,400
COX-2 First	£740.99	£290.70	3.21960	0.00828	£35,100

Except where otherwise stated, ICER for each option is relative to the previous option listed. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY).

Table 82: Results with relative risk for all types of GI event at the upper confidence limits (favouring non-selective NSAIDs)

Etodolac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£476.43		3.19748		
COX-2 Second	£526.40	£49.97	3.19387	-0.00361	(Dominated)
COX-2 First	£825.86	£299.46	3.19242	-0.00145	(Dominated)

ICER for "COX-2 First" relative to "No COX-2"

Except where otherwise stated, ICER for each option is relative to the previous option listed. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY).

Varying risk of MI

For each COX-2 selective NSAID separately, we varied the relative risk of MI (compared to ibuprofen) across its 95% confidence limits shown in Table 70. Results for all drugs are reported in full in Appendix 10. Again the results relating to Etodolac are reported here for illustration only – for the lower limits in Table 83 and for the upper limits in Table 84. In the absence of data, we assumed that the risks for etodolac and meloxicam were the same as for celecoxib. Here, we have used the confidence limits for celecoxib as well. This gives reasonable coverage of the range of values for COX-2 selective NSAIDs. In general terms, the results are sensitive to variation in the value of the risk of MI events.

Table 83: Results with relative risk for MI at the lower confidence limits (favouring COX-2 selective NSAIDs)

Etodolac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		

COX-2 Second	£485.04	£43.80	3.20445	0.00017	£257,000
COX-2 First	£770.83	£285.78	3.21018	0.00573	£49,900

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£441.25		3.20428		
COX-2 First	£770.83	£329.58	3.21018	0.00590	£55,900

Except where otherwise stated, ICER for each option is relative to the previous option listed. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY).

Table 84: Results with relative risk for MI at the upper confidence limits (favouring non-selective NSAIDs)

Etodolac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£488.76	£47.51	3.20391	-0.00037	(Dominated)
COX-2 First	£796.43	£355.18	3.20646	0.00219	£162,000

ICER for "COX-2 First" relative to "No COX-2"

Except where otherwise stated, ICER for each option is relative to the previous option listed. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY).

As a separate analysis, we tested the view that NSAIDs do not protect against MI: this was done by setting the "No NSAID" risk for MI to be 0.23/100 person years, the same as the better non-selective NSAID (diclofenac). This made very little difference to the base case results (see Appendix 10).

5.6.3 Results for high risk patients

The most important high risk group consists of patients with previous GI history. For these patients, the comparison is between COX-2 selective NSAIDs (taken originally without PPI) and non-selective NSAIDs taken with PPI. The results are shown in Table 85.

Table 85: Results for patients with previous GI history

Celecoxib (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
COX-2 Second	£734.85		3.21016		
No COX-2	£752.74	£17.89	3.21635	0.00619	£2,890
COX-2 First	£995.11	£242.37	3.2029	-0.01346	(Dominated)

Celecoxib (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£752.74		3.21635		
COX-2 Second	£789.88	£37.14	3.21016	-0.00619	(Dominated)
COX-2 First	£1,591.11	£838.37	3.2029	-0.01346	(Dominated)

Etodolac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
COX-2 Second	£714.39		3.21193		
No COX-2	£752.74	£38.35	3.21635	0.00442	£8,670
COX-2 First	£816.49	£63.75	3.20826	-0.00809	(Dominated)

Etoricoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
COX-2 Second	£710.21		3.21431		
No COX-2	£752.74	£42.54	3.21635	0.00205	£20,800
COX-2 First	£1,008.46	£255.72	3.21774	0.00138	£185,000

Meloxicam (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
COX-2 First	£666.72		3.2093		
COX-2 Second	£703.14	£36.42	3.21186	0.00256	£14,200
No COX-2	£752.74	£49.60	3.21635	0.00450	£11,000
Excluding the option "COX-2 Second" (by extended dominance):					
COX-2 First	£666.72		3.2093		
No COX-2	£752.74	£86.02	3.21635	0.00706	£12,200

Meloxicam (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
COX-2 Second	£713.17		3.21186		
No COX-2	£752.74	£39.57	3.21636	0.0045	£8,800
COX-2 First	£774.90	£22.16	3.20930	-0.00706	(Dominated)

Rofecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
COX-2 Second	£739.93		3.21118		
No COX-2	£752.74	£12.81	3.21635	0.00517	£2,480
COX-2 First	£1,079.21	£326.46	3.20557	-0.01079	(Dominated)

Valdecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
COX-2 Second	£721.59		3.21444		
No COX-2	£752.74	£31.16	3.21635	0.00192	£16,200
COX-2 First	£995.31	£242.57	3.21742	0.00106	£228,000

Except where otherwise stated, ICER for each option is relative to the previous option listed. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY).

Once again, these results are broadly consistent with those reported in Table 76 and Table 77 for the analyses using the simpler AGM. If we look first at the results relating to celecoxib in OA, they indicate that its use second line (after initially trying ibuprofen) is associated with a lower cost but also reduced effectiveness when compared to the 'No COX-2' strategy (i.e.

ibuprofen followed by diclofenac, if required). This gives an ICER of £2,890 for the move from the strategy of celecoxib second line to the strategy of no COX-2. It is clearly not cost-effective to use celecoxib either first or second line according to these results. All strategies relating to the use of COX-2 drugs (both first and second line use) look very unattractive from a cost-effectiveness point of view for all of the drugs considered here.

5.7 Summary

- The Assessment Group has undertaken a new modelling exercise that used the Markov model developed originally by Maetzel et al (2001) as a starting point.
- The model has been designed to run in two different forms: the 'full AGM', which includes an initial drug switching cycle, and the 'simpler AGM', where there is no initial cycle and no opportunity for the patient to switch NSAID.
- The main data sources for clinical parameters are the meta-analysis results from our systematic review. Where necessary, we have used other sources.
- Using the simpler AGM, with ibuprofen or diclofenac alone as the comparator, all of the COX-2 products are associated with higher costs (i.e. positive incremental costs) and small increases in effectiveness (i.e. positive incremental effectiveness), measured in terms of QALYs. The magnitude of the incremental costs and the incremental effects, and therefore the ICERs, vary considerably across all COX-2 drugs.
- When the simpler AGM was run using ibuprofen or diclofenac combined with PPI as the comparator, the results change substantially, with the COX-2 drugs looking generally unattractive from a cost-effectiveness point of view. This applies both to standard patients and to "high-risk" patients defined in terms of previous GI events.
- The full model produced results broadly in line with the simpler model.

6 IMPLICATIONS FOR OTHER PARTIES

RA and OA are common chronic conditions that have a substantial negative impact on the quality of life of sufferers. In addition to healthcare costs, arthritis is associated with considerable indirect costs incurred by patients and carers as the result of forgone paid work, and forgone leisure time. Although the difference in pain relief between conventional NSAIDs and COX-2 selective NSAIDs is likely to be small, differences in GI tolerability of NSAIDs and serious GI events, if realised, would have important quality of life implications for patients.

7 FACTORS RELEVANT TO NHS

A principle implication of switching from conventional NSAIDs to COX-2 selective NSAIDs for the management of individuals with OA and RA is drug cost and increased budget impact. Healthcare professionals need to be able to clearly identify the precise role of COX-2 selective NSAIDs in OA and RA to maximise health. Current NICE guidance recommends the use of COX-2 selective drugs in *high risk* individuals (i.e. age ≥ 65years; previous history of GI events; patients taking concomitant anticoagulants or corticosteroids) with OA and RA. Individuals not at high risk are recommended to remain on conventional NSAIDs.

The poor adherence to current guidelines in audits of routine practice, described in the introduction of this report, highlights the potential limitations of these guidelines. Clinicians prescribing drugs often make judgements about risks and benefits and chose drugs based on personal knowledge of individual patients and their preferences, professional experience, and nuances of medical history. These factors cannot be incorporated readily into guidelines.

8 DISCUSSION

8.1 Main results

The purpose of this report was to assess the effectiveness and cost effectiveness of COX-2 selective NSAIDs (celecoxib, etodolac, etoricoxib, meloxicam, rofecoxib, and valdecoxib) for the management of patients with OA and RA.

8.1.1 Clinical effectiveness

Our review, which supports data in other reviews, showed that COX-2 selective NSAIDs are generally equivalent to non-selective NSAIDs for the symptomatic relief of RA and OA. Meloxicam appears to be less effective for pain than non-selective NSAIDs particularly piroxicam, although this finding is very likely a result of inappropriate dose comparisons in trials.

Celecoxib, rofecoxib and valdecoxib significantly reduced both PUBs and POBs compared to non-selective NSAIDs. We have not shown this for other COX-2 selective NSAIDs - our analysis failed to reach statistical significance. This may reflect absence of evidence, particularly for newer COX-2 selective agents, rather than evidence of absence. The magnitude of UGI benefits for COX-2 selective NSAIDs appear similar, for example, for PUBs: celecoxib RR 0.64 (95% CI: 0.46 to 0.89); rofecoxib 0.43 (95% CI: 0.32 to 0.57); meloxicam RR: 0.50 (0.25 to 1.08); etoricoxib RR: 0.23 (95% CI: 0.05 to 1.08); valdecoxib RR: 0.12 (95% CI: 0.03 to 0.59); and etodolac RR: 0.32 (95%CI: 0.15 to 0.71). Nevertheless these comparisons should be interpreted with caution as they are based on differing amounts of evidence, concerns about appropriate doses of COX-2 selective NSAIDs especially meloxicam and are indirect

comparisons. There are many potential confounding differences in the patient populations included such as the use of concomitant therapies, choice and dosage of comparator NSAIDs, and methods of assessing outcomes. The remarkable heterogeneity of non-selective NSAIDs in their ability to cause serious UGI events in observational studies also raises concerns about comparisons based on meta-analyses of single COX-2 selective NSAID versus a basket of non-selective NSAIDs [reference needed].

A proportion of patients at high risk are included in some trials but many studies excluded higher risk patients, for example those on low dose aspirin. This limits the generalisability of some trials. Certain individuals such as those with a previous peptic ulcer have a higher risk of further bleeding regardless of NSAID use. Post-hoc and sub-group analyses have been included in some reports such that, for example: the GI protective effect of celecoxib is independent of age (≤65 yrs vs >65 yrs), *H. Pylori* status, low dose aspirin use, and steroid use. However analyses are based on relatively small numbers of patients. A direct comparison of celecoxib with diclofenac combined with omeprazole in patients with a recent GI bleed did not show any significant differences although the wisdom of giving any NSAIDs to some patients in this category is questionable.

We have shown that patients on a number of the COX-2 selective NSAIDs significantly increase the risk of MI compared with those on non-selective NSAIDs, especially naproxen, strongly supporting other data indicating a cardio-protective effect of non-selective NSAIDs compared with placebo; presumably through inhibition of platelet activity.[305,306]

8.1.2 Cost effectiveness

Review of cost-effectiveness literature

A systematic review of the cost-effectiveness literature on COX-2 selective NSAIDs has been undertaken. The results of published economic evaluations are highly variable. Virtually all analyses made use of a decision analytic model. Published models vary in some important aspects (e.g. whether switching of therapy is considered, timeframe, nature of events considered, etc.) making direct comparisons difficult. Studies that explicitly considered cardiovascular events were generally less favourable to COX-2 selective NSAIDs. Economic analyses that modelled costs and benefits over a relatively short period (usually between 6 and 12 months) tended to favour COX-2 selective NSAIDs; but, analyses allowing a longer time horizon, for example between 5 years and a patient's lifetime, found incremental cost-effectiveness ratios that were considerably higher. Where restricted use of COX-2s was considered as part of the analysis, for example to high risk patients, cost-effectiveness was more favourable.

Review of industry submissions

Industry submissions including a formal economic evaluation were received from three companies: Pfizer, Merck Sharp & Dohme and Boehringer Ingelheim. All three used a decision modelling approach, although the models vary in some important aspects; so, direct comparisons are, again, difficult. Analyses all compared COX-2 selective NSAIDs with a non-selective NSAID strategy (in some cases with co-therapy). Results, if taken at face value, support the widespread use of celecoxib, rofecoxib, meloxicam, etoricoxib and valdecoxib. None of the analyses report direct comparisons of different COX-2 selective NSAIDs but all, consistently, found, in sensitivity analyses, that cost-effectiveness was more favourable when drug use was restricted to 'high risk' patients and when the COX-2 selective NSAIDs had a large beneficial effect on UGI events.

Assessment Group Model
Our own model was an extension of the model developed by Maetzel et al (2001)[282]. We added an initial cycle allowing for early switching of drugs, in order to reflect, more accurately, the patterns of NSAID use in primary care. Subsequent cycles largely follow the original Maetzel model structure. Initial cycle probabilities are mainly based on Langman et al (2001)[307], who reported on patterns of NSAID use in a large cohort of primary care patients. For the main Markov cycles we have used the results from our own systematic review, where possible.

Our model shows, that in comparison to non-selective NSAIDs, the various COX-2 selective NSAIDs considered in this report are associated with a wide range of costs per quality adjusted life year gained (QALY) in arthritis patients. Cost per QALY differed for each COX-2 selective agent, whether the drug was to be used for a 'standard' patient or a high risk patient (one with a previous GI ulcer or bleed), the choice of non-selective NSAID comparator, and whether the non-selective NSAID was used in combination with a PPI.

8.2 Assumptions, limitations and uncertainties

A key strength of our report was its comprehensiveness – we identified and included more trials than previous systematic reviews – and direct integration of the results of the systematic review into the assessment group basis. In addition, we were able to include a number of direct comparisons between COX-2 selective NSAIDs; published recently. The latter, particularly for rofecoxib and celecoxib, show similar efficacy between agents but direct comparisons with adequate power, using comparable doses, and of sufficient duration are needed to clearly understand safety issues.

Some other limitations in the evidence were identified:

1) Outcomes examined by trials are relatively broad and sometimes poorly defined, particularly for older studies, increasing the potential for bias in the reporting and analysis of data. For example, in most trials, the PUB category did not provide specific data about the frequency of perforations, gastric outlet obstructions, or GI bleeds associated with heamodynamic instability or hospitalisation because of these adverse events.
2) Many studies did not report adverse events adequately or; perhaps worse, mentioned several events in an ad hoc manner, so that, when collated, events may not have reflected their actual occurrence or allowed meaningful comparisons between drugs used.
3) The non-selective NSAID preferred in many studies, naproxen, reflects preferences in the US where naproxen is used widely. In England and Wales diclofenac and ibuprofen predominate. In some studies the choice and dose of non-selective NSAID comparator, and limited details of the population studied (for example aspirin use and prior GI history) make it difficult to generalise this evidence base to routine clinical practice.
4) Age restrictions and other exclusion criteria also limit generalisability supporting the case for more pragmatic studies. A variety of observational data clearly shows the limitations of NSAIDs in clinical practice. Trials reported here invariably included individuals who were established and accepting of NSAIDs and indeed required a *flare* of symptoms on NSAID withdrawal before inclusion. This biases toward, not only inflated figures on drug retention with chronic therapy, but also a greater likelihood of response to any therapy on the basis of spontaneous improvement of symptoms after a flare (regression to the mean).

Potential limitations of our review:

1) According to the assessment criteria used, the majority of included trials were judged to be of 'good' to 'excellent' quality i.e. appropriate randomisation and concealment, double blinding and low loss to follow up. However, despite selective inclusion criteria, there was often considerable attrition in many trials because of adverse events and lack of efficacy. This attrition varied for different drugs so, for example, in the CLASS study 47% and 41% of patients completed the trial at 52 weeks from the celecoxib and non-selective NSAID (diclofenac and ibuprofen) arms, respectively. As a result, there is less patient 'exposure' to non-selective NSAID than celecoxib in the initially randomised groups. By implication this would favour NSAID patients for GI safety outcomes. This is overcome, however, by presenting data that allows for differing durations of drug exposure.
2) The quality, and amount of evidence for newer COX-2 selective drugs was generally far greater than for older drugs, particularly in terms of long-term GI and CV safety. This, and the heterogeneity of outcome data for selective and non-selective NSAIDs (indicated by observational studies) raise a question about, conceptually, considering NSAIDs simply as two separate classes of agents.
3) For accuracy we relied on full study reports for data. However, trial reports from drug sponsors were not available universally. For example, most celecoxib trials study reports were available; but in contrast no industry study reports were available for etodololac and meloxicam. This may have lead to unforeseen biases.

There are a number of potential limitations of the cost effectiveness analysis undertaken in this report, including issues of model structure and model parameters:

1) The majority of models developed for arthritis specifically exclude consideration of adverse events other then GI events and MI risk and therefore does not take into account differences in GI tolerance or efficacy between drugs. Nor do published models allow differences between agents in other adverse events such as skin rashes or hepatitis. As an adaptation of the Maetzel model, our model used is similar in this respect; but, the initial ('switching') cycle added to our model allows drug switching and therefore does takes into account, to some extent, drug changes including withdrawal for lack of efficacy or adverse events.
2) The model only allows one clinical event possible in each cycle (i.e. an arthritis patient cannot undergo MI and a serious GI event within same Markov cycle).
3) Our model, in common with other published models does not consider drug compliance and the tendency for many patients to use NSAIDs intermittently rather than continuously.
4) Relatively limited observational data were available to populate the initial (switching) cycle of the model.
5) Clinical GI events and MI risk for comparator NSAIDs used in the model were based on data from patients in CLASS not taking aspirin. In contrast, the model used relative risks of clinical GI events and MI for the COX-2 selective agents were based on meta-analysis that includes all trial patients (i.e. both aspirin users and non users). Nevertheless, evidence from our clinical review indicates that effect of COX-2 on GI events and MI risk is maintained, regardless of aspirin status.

The utility values used are based on those reported by Maetzel report using a sample of the general public and the standard gamble method. Although, this a recognised approach to the derivation of utility values, it is has been pointed out that the method may underestimate the severity of short-term effects[282].

8.3 Need for further research

Clinical evidence is still lacking for many areas related to the use of COX-2 selective NSAIDs for OA and RA patients. Further research addressing the following issues would be particular valuable for clinical practice and policy decision-making:

1) Additional trial evidence in order to confirm the safety of etodolac, meloxicam, etoricoxib, and valdecoxib in terms of clinical GI events and serious cardiovascular events.
2) Trials that assess the relative costs, efficacy and safety effects:
    a. Of COX-2 selective NSAIDs versus combination of non-selective NSAIDs and gastroprotective agent in people at 'standard' risk and those at a higher risk
    b. Of different COX-2 selective NSAIDs directly compared using equivalent doses
    c. Of lower doses of non-selective NSAIDs, for example ibuprofen 1200 mg per day, which are routinely used in clinical practice;
    d. And include patients with differing cardiovascular and GI risks including those on aspirin and, particularly older age groups likely to need NSAIDs.
    e. Patients with differing types and severities of OA.

Further observational studies that describe patterns of drug use by informed patients with OA and RA including switching between agents.

9 CONCLUSIONS

In comparison to non-selective NSAIDs, COX-2 selective NSAIDs are more expensive and economic modelling shows a wide range of possible costs per quality adjusted life year gained (QALY) in patients with osteoarthritis and rheumatoid arthritis. Costs per QALY also varied if individual drugs were used in 'standard' or 'high'-risk patients, the choice of non-selective NSAID comparator and whether that NSAID was combined with a PPI.

10 APPENDICES

Appendix 1: Review of existing systematic reviews

1. Characteristics of the included reviews

The characteristics of included systematic reviews are summarised in Table 86, pg 174. Of the completed reviews thirteen evaluated celecoxib, five etodolac, seven meloxicam, eleven rofecoxib and one valdecoxib. No systematic reviews for lumiracoxib or etroricoxib were found. All reviews evaluated use in patients with RA or OA. Some reviews also included other pain-related conditions such as dental pain and primary dysmenorrhea. Four reviews evaluated use in patients with RA only and four in patients with OA only. Thirteen reviews evaluated both efficacy and safety outcomes, five focused on tolerability and safety (GI safety in all cases but one), and two on efficacy.

Twelve reviews were narrative reports: providing a qualitative synthesis of included studies. Only six undertook a meta-analysis.[113,121,122,125,126,131] The remaining two planned a meta-analysis but did not do so because of insufficient data.[112,119]

2. Quality of Reviews

The quality of reviews was assessed according to Oxman and Guyatt's criteria.[308] These criteria assess the adherence of a review to scientific principles known to reduce bias. An overall score is assigned out of 7, where 1 represents 'extensive flaws in the scientific quality of the overview', 3 'major flaws', 5 'minor flaws' and 7 'minimal flaws'.

The quality of included reviews is summarised in Table I below. Most included reviews scored 3 (4 reviews) or 4 (6 reviews) - indicating major or moderate flaws. These were related to potential bias in the selection of studies,[120,123] publication,[121,129] language,[114,117,121,124,125,127,129] geographical bias,[114] lack of evaluation and analysis of the quality of included studies,[114,117,121,122] and lack, or only partial reporting, of methods for combining data from studies.[114,120,123-125,127,129] For example, the review by Deeks and colleagues of celecoxib[113] was methodologically of very high quality but failed to identify different publications as originating from the same study population and proceeded to pool duplicate data from these same studies, leading to bias.

A further five reviews[115,116,118,128,130] scored 2 on quality assessment, indicating major flaws. These poor quality reviews did not show clearly a comprehensive search strategy or that precise inclusion criteria had been applied.

Overall only four of the included reviews were considered to be of the highest quality (i.e. quality score of 7).[112,119,126,131]

3. Results

Efficacy

All reviews gave a narrative of efficacy data: Deeks and colleagues direction of bias[113] did a meta-analysis - the pooled summary estimates from this study were prone to bias as discussed

above. Nevertheless this review, like others, concluded that the efficacy of celocoxib was similar to non-selective NSAIDs. Most reviews, except Emery and colleagues, separated OA and RA patients and since outcome measures and patient characteristics may differ substantial pooling may not be appropriate.

Eleven reviews[112-114,116,118-120,124,130,131,309] evaluated the efficacy of COX-2 selective NSAIDs for RA; 7 celecoxib,[112-114,116,127,130,131] 2 etodolac,[124,131] 4 meloxicam,[114,116,124,131] 6 rofecoxib,[114,116,118,119,130,131] and 1 valdecoxib.[120]

Eleven reviews[113-116,118,120,124,125,128,129,131] evaluated the efficacy of COX-2 selective NSAIDs for OA; 6 celecoxib,[113-116,128,131] 4 etodolac,[124,125,129,131] 4 meloxicam,[114,116,124,131] 6 rofecoxib,[114-116,118,128,131] and 1 valdecoxib.[120]

Emery et al[124] evaluated the relationship between NSAID dose, for etodolac, meloxicam and non-selective NSAIDs, and efficacy in patients with RA or OA. Overall meloxicam 7.5mg and 15mg were considered more effective than placebo with the 15mg dose superior to 7.5mg for efficacy. Results for etodolac were less clear. One trial suggested improved efficacy with etodolac 300mg twice a day compared with 200mg twice a day, but a second trial found no statistically significant difference between doses.

Celecoxib
All reviews of celecoxib, except one which did not report efficacy data in OA,[116] reported superior efficacy to placebo and comparable efficacy to non-selective NSAIDs in OA and RA.[112,114-116,127,128,130,131] Additionally Schitzer concluded that celecoxib was superior to paracetamol for OA.[115]

Etodolac
The previous HTA report for NICE for NICE showed that etodolac was comparable to non-selective NSAIDs including aspirin, piroxicam and ibuprofen in RA: no comparisons with placebo were reported.[131] In OA, etodolac was more efficacious than placebo,[125,129,131] and comparable to diclofenac,[125,129,131] naproxen,[125,129,131] piroxicam,[129,131] nimesulide,[131] and tenoxicamin.[131] Two reviews suggested etodolac may be more effective than indomethacin[129] and nabumetone.[131]

Meloxicam
Two reviews provided data on the efficacy of meloxicam in RA.[116,131] A third concluded that meloxicam was significantly more effective than placebo and comparable to non-selective NSAIDs.[114] Meloxicam was more efficacious than placebo[131] and equivalent to diclofenac[114,131] piroxicam[116,131] and naproxen[114] in OA.

Rofecoxib
Three reviews concluded that rofecoxib was superior to placebo[118,119,131] and of comparable efficacy to naproxen in RA.[119,131] In OA, rofecoxib was superior to placebo[118,128,131] and paracetamol[115] and of comparable efficacy to diclofenac,[114-116,118,128] ibuprofen (high dose)[114-116,118,128] naproxen[115] and nabumetone[118]

Valdecoxib
One review reported that valdecoxib (doses range 10 to 40mg daily) was superior to placebo and of comparable efficacy to naproxen in OA and RA.[120]

Table 86: Characteristics of included systematic reviews

Review identifier	COX 2 evaluated	Disease population	Outcome domains	Number of trials included (n=pts)	Meta-analysis	Quality Score*	Comments
Ashcroft 2001 [122]	Celecoxib	RA & OA	Safety- GI	5 (n=4632)	Yes	4	Included RCTs w incidence of endo as RRs. If chi squ used. Some of the Sensitivity analys
Chavez 2003 [120]	Valdecoxib	Any	Efficacy Safety Pharmacology Kinetics	RA & OA 7 (n=6385) + 2 SR	No	3	Narrative review. (majority were ab is presented but c
Deeks 2002 [113]	Celecoxib	RA & OA	Efficacy Safety Tolerability	9 (n=15,187)	Yes	4	Systematic review included from ma Separate meta-an outcome. Duplicate data fro inappropriately.
Desoky 2001 [130]	Celecoxib Rofecoxib	RA	Efficacy Safety Kinetics interactions	3 Celecoxib (n>8,700) + 2 SRs + manu info 0 Rofecoxib + manu info	No	2	Narrative review studies not specif
Emery 2002 [124]	Meloxicam Etodolac	RA & OA	Efficacy Safety	10 Meloxicam (n=3351) +1 SR 7 Etodolac (n=3411) + 1 SR	No	4	Narrative review and safety. Searc open label & non selective NSAID question posed.
Garner 2002 [119]	Rofecoxib	RA	Efficacy Safety	2 (n =8,734)	No due to lack of data	7	Review of RCTs Statistical poolin paucity of data.
Garner 2002 (cele) [112]	Celecoxib	RA	Efficacy Safety	5 (n=4465)	No due to lack of data	6	Review of publis weeks. Three stu pool results of st
Hogue 2002 [128]	Celecoxib Rofecoxib	OA	Efficacy Safety	4 Celecoxib (n=9626) + 1 SR 8 Rofecoxib (n>11,900)	No	2	Narrative review first line treatmer NSAIDs &COX-
Kaplan-Machalis 1999 [114]	Celecoxib Rofecoxib Meloxicam	Any	Efficacy Safety Kinetics Cost	1 Celecoxib (n=330)+ man info 2 Rofecoxib (n=1,520) + man info 10 Meloxicam (n=20,857) +1 SR	No	3	Narrative review NSAIDs. Include ranging trials in I trials. Data on ce manufacturers pr limited in 1999.

Review identifier	COX 2 evaluated	Disease population	Outcome domains	Number of trials included (n=pts)	Meta-analysis	Quality Score*	Comments
Luong 2000[127]	Celecoxib	RA	Efficacy, safety, kinetics, cost interactions,	4 (n=3233)	No	3	Narrative review English. Majority
Mukherjee 2001 [117]	Celecoxib Rofecoxib	Any	Safety (cardiovascular events)	1 celecoxib(n=7968) 3 rofecoxib (n= 10,096)	No	4	Narrative review in COX-2 trials (placebo group of prevention trials
NICE 2000 Addendum 2001 [131]	Celecoxib Rofecoxib Meloxicam Etodolac	RA & OA	Efficacy and Safety Cost-effectiveness	77 n=61731 16 celecoxib (n>15770) + 1 SR 15 rofecoxib (n=16512) 3 celecoxib and rofecoxib (n=1374) 13 meloxicam (n=22080) 30 etodolac (n=5352)	Yes but only for AEs	7	Included systema report was updat data for AEs poo available – consi
Rostom A2003 [126]	Celecoxib Rofecoxib Meloxicam	RA, OA or other arthritic condition	Safety- GI	10 celecoxib- (n=28169) + 1 MA 12 rofecoxib (n=19913) + 1 MA 3 Celecoxib & rofecoxib (n=1375) 10 meloxicam (n=21421) + 1 MA	Yes	7	Included RCTs a toxicity of COX- gastroprotection. model. Sensitivit
Schnitzer 2001 [115]	Celecoxib Rofecoxib	OA	Efficacy Safety Cost	5 Celecoxib (n >11,000) + 3 SR + man info 10 Rofecoxib (n>13,000) + 3 SRs + man info 1 celecoxib and rofecoxib (n=382)	No	2	Narrative review the management not specified.
Schoenfeld 1999[121]	Meloxicam	Any	Safety- GI	RA & OA 9 (n>20,022) + 1 SR	Yes	3	Included English of frequency of e explored.
Symmons 2002	Not specified	Not specified	Efficacy Safety Cost-effectiveness	?	?	na	Included RCTs. I NSAID induced report.

Review identifier	COX 2 evaluated	Disease population	Outcome domains	Number of trials included (n=pts)	Meta-analysis	Quality Score*	Comments
Towheed 1997[129]	Etodolac	OA knee	Efficacy	10 etodolac (n=1090)	No	3	Narrative review studies, publishe Difficult to extra
Vasoo 2001 [116]	Celecoxib Rofecoxib Meloxicam	Any	Efficacy Safety	2 Celecoxib (n=8714) + 1 SR 3 Reofecoxib (n>1500) + 1 SR 2 Meloxicam (n=17979) +1 SR	No	2	Narrative review provide an updat
Vreis de 2002 [123]	Celecoxib Rofecoxib Meloxicam Etodolac	RA & OA	Safety –GI	2 Celecoxib - (n=1137) 1 Rofecoxib - (n=483) 3 Meloxicam - (n=1075) + 1 SR (NICE)	No	4	Included RCTs a summarised plus was a second rep
Watson 1996 [125]	Etodolac	OA knee	Efficacy – relative of individual NSAIDs	11 etodolac (n>1300)	Planned	4	Included RCTs i NSAIDs licensed Only withdrawal vs diclofenac, na
Weaver 2001 [118]	Rofecoxib	Any	Efficacy Safety	RA & OA 9 (n=12365)+ 2 reviews	No	2	Narrative review of studies includ

* On a scale where 1=extreme flaws to 7=minimal flaws

Eleven reviews[113-116,118,120,124,125,128,129,131] evaluated the efficacy of COX-2 selective NSAIDs for OA; 6 celecoxib,[113-116,128,131] 4 etodolac,[124,125,129,131] 4 meloxicam,[114,116,124,131] 6 rofecoxib,[114-116,118,128,131] and 1 valdecoxib.[120]

Emery et al[124] evaluated the relationship between NSAID dose, for etodolac, meloxicam and non-selective NSAIDs, and efficacy in patients with RA or OA. Overall meloxicam 7.5mg and 15mg were considered more effective than placebo with the 15mg dose superior to 7.5mg for efficacy. Results for etodolac were less clear. One trial suggested improved efficacy with etodolac 300mg twice a day compared with 200mg twice a day, but a second trial found no statistically significant difference between doses.

Celecoxib (see Table 87, pg 179)
All reviews of celecoxib, except one which did not report efficacy data in OA,[116] reported superior efficacy to placebo and comparable efficacy to non-selective NSAIDs in OA and RA.[112,114-116,127,128,130,131] Additionally Schitzer concluded that celecoxib was superior to paracetamol for OA.[115]

Etodolac (see Table 88, pg 181)
The previous HTA report for NICE for NICE showed that etodolac was comparable to non-selective NSAIDs including aspirin, piroxicam and ibuprofen in RA: no comparisons with placebo were reported.[131] In OA, etodolac was more efficacious than placebo,[125,129,131] and comparable to diclofenac,[125,129,131] naproxen,[125,129,131] piroxicam,[129,131] nimesulide,[131] and tenoxicamin.[131] Two reviews suggested etodolac may be more effective than indomethacin[129] and nabumetone.[131]

Meloxicam (see Table 89, pg 183)
Two reviews provided data on the efficacy of meloxicam in RA.[116,131] A third concluded that meloxicam was significantly more effective than placebo and comparable to non-selective NSAIDs.[114] Meloxicam was more efficacious than placebo[131] and equivalent to diclofenac[114,131] piroxicam[116,131] and naproxen[114] in OA.

Rofecoxib (see Table 90, 184)
Three reviews concluded that rofecoxib was superior to placebo[118,119,131] and of comparable efficacy to naproxen in RA.[119,131] In OA, rofecoxib was superior to placebo[118,128,131] and paracetamol[115] and of comparable efficacy to diclofenac,[114-116,118,128] ibuprofen (high dose)[114-116,118,128] naproxen[115] and nabumetone[118]

Valdecoxib (see Table 91, pg 186)
One review reported that valdecoxib (doses range 10 to 40mg daily) was superior to placebo and of comparable efficacy to naproxen in OA and RA.[120]

Table 87: Celecoxib studies in patients with OA or RA included in each systematic review

Trial identifier	Kaplan-Machilis 1999[114]	Luong 2000 [127]	NICE 2000/1 [131]	Ashcroft 2001 [122]	Desoky 2001 [130]	Mukherjee 2001 [117]	Schnitzer 2001 [115]	Vasoo 2001 [116]	Deeks 2002 [113]	Garner 2002 Cele [112]	Hogue 2002 [128]			
Bensen 2000[93]			✓				✓				✓			
Bensen 1999[139,140] Pf Study 020			✓				✓		✓		✓			
Chan 2002 [58]														
Clemett 2000[310] Review					✓									
Emery 1999[154] Pf Study 041		✓	✓	✓	✓		✓	✓	✓	✓				
Geba 2002[263] VACT-1			✓				✓				✓			
Gibovsky 2003 [311] Pf Study 003														
Goldstein 2000[94]					✓		✓	✓						
Goldstein 2001[164] Pf Study 062			✓	✓					✓	✓				
Goldstein 2001 Pf Study 096 SUCCESS-1														
Hawel 2003 [312]														
Kivitz 2001 [313] Geis 1999b Pf study 054			✓ CIC						✓ DOF					
Lipsky 1997[314]					✓									
Mc Kenna 2001a[146] Pf Study 118			✓ CIC											
McKenna 2001b[145] Pf Study 152			✓								✓			
McKenna 2002 [315] Pf Study 042			✓ CIC											
Pf Study 021		✓	✓ CIC	✓ FDA										
Pf Study 023			✓ CIC											
Pf Study 047			✓ CIC											
Pf Study 071		✓	✓ CIC	✓ FDA					✓ DOF					
Pf Study 105														
Pf Study 106														
Pf Study 107														
Pf Study 209														
Pf Study 210														
Pf Study 211														

Trial identifier	Kaplan-Machilis 1999[114]	Luong 2000 [127]	NICE 2000/1 [131]	Ashcroft 2001 [122]	Desoky 2001 [130]	Mukherjee 2001 [117]	Schnitzer 2001 [115]	Vasoo 2001 [116]	Deeks 2002 [113]	Garner 2002 Cele [112]	Hogue 2002 [128]			
Pf Study 212														
Pincus 2003[316], PACES-a Pf Study 010														
Pincus 2004[317], PACES-b Pf Study 249														
Silverstein 2000[159] Pf study 102 –CLASS			✓		✓	✓	✓	✓	✓	✓	✓			
Simon 1998a[138] Pf study 012	✓	✓	✓ CIC				✓			✓				
Simon 1998b[318] Pf Study 013														
Simon 1999[155] Pf study 022		✓	✓ CIC	✓			✓		✓	✓				
Sowers 2003, CRESCENT Pf Study 002														
Suarez-Otero 2002 [319]														
Whelton 2001[260] SUCCESS V1, Pf Study 149			✓											
Whelton 2002 [320] Pf Study 181														
Williams 2000[142] Pf Study 060			✓ CIC											
Willams 2001[321] Pf study 087			✓ CIC											

DOF Data on file
FDA Reports available on FDA website
CIC commercial in confidence
*Studies excluded due to: [a]pooled analysis; [b]narrative review

Table 88: Studies with etodolac in patients with RA or OA included in each

Trial Ref	Watson 1996 [125]	Towheed 1997 [129]	NICE 2000/1 [131]	Emery 2002 [124]	Vries 2002 [123]	WMHTAC 2004
Andelman 1983[322]						*[a]
Bacon 1990 [323] **6 trials**						✓(3) *(3)[a]
Bianchi Porro 1991[324,325]			✓			*[a]
Brasseur 1991[221]	✓	✓				✓
Briancon 1991[326]			✓			*[a]
Burssens 1993[327]						✓
Chikanza 1994[232]			✓			✓
Ciompi 1989[328]			✓			*[b]
De Queiros 1991[329]			✓			*[a]
Del Toro 1983[330]			✓			*[a]
Delcambri 1990[331]						✓
Dick 1992[227]	✓	✓	✓			✓
Dick 1993[332]			✓			*[a]
Dore 1995[235]	✓			✓		✓
Edwards 1983[333]			✓			*[a]
Eisenkolb 1993 [231]	✓		✓			✓
Fioravanti 1989[334]						*[a]
Freitas 1990[220]		✓				✓
Gordon 1983[335]			✓			*[a]
Grisanti 1992 [228]	✓	✓	✓			✓
Jacob 1983[336]			✓	✓		*[a]
Jacob 1985a[337]			✓			*[a]
Jacob 1985b[338]						*[a]
Jacob 1986[339]			✓			*[a]
Jennings 1997[340]						✓
Jubb 1992 [341]				✓		*[c]
Karbowski 1991 [222]	✓	✓				✓
Khan 1992[342]		✓				*[c]
Liang 2003[343]						*[a]
Lightfoot 1997[243]			✓	✓		✓
Lonauer 1993[344]			✓			*[a]
Lucker 1994[233]			✓			✓
Neustadt 1997[244]			✓	✓		✓
Palferman 1991 [223]	✓	✓				✓
Paulsen 1991[224]	✓	✓	✓			✓
Pena 1991 [225]	✓	✓				✓
Perpignano 1991[345]						✓
Perpignano 1994[234]			✓			✓
Porzio 1993[346]			✓			*[a]
Rogind 1997[238]			✓			✓
Sanda 1983[347]						*[a]
Schattenkirchner 1990[105]				✓		*[d]
Schattenkirchner 1991[348]			✓			*[a]
Schnitzer 1995 [236]	✓		✓	✓		✓
Schnitzer 1997[239]				✓		✓
Taha 1989[240]			✓			✓
Taha 1990[242]			✓			✓
Vetter 1982[349]			✓			*[e]
Waltham-Weeks 1987[350]			✓			*[a]
Waterworth 1992 [229]	✓					✓

Trial Ref	Watson 1996 [125]	Towheed 1997 [129]	NICE 2000/1 [131]	Emery 2002 [124]	Vries 2002 [123]	WMHTAC 2004
William 1989[219]		✓	✓			✓

Studies listed are those included in each review to evaluate efficacy and/or safety in patients with RA or OA. Studies in other patient populations are not listed. Reviews/meta-analyses are listed where they formed part of the analysis of efficacy and/or safety. Those referred to just in the introduction or discussion are not listed
*Studies excluded due to: [a]sub-license doses, [b]duration of treatment less than 2 weeks, [c]interim trial reports, [d]pooled analysis, [e]inappropriate design

Table 89: Studies with meloxicam in patients with RA or OA included in each systematic review

Trial Ref	Kaplan-Machilis B 1999[114]	Schoenfeld 1999 [121]	NICE 2000/1 [131]	Vasoo 2001 [116]	Emery 2002 [124]	Vries 2002 [123]	Rostom 2003 [126]	WMHTAC 2004
Carraba 1995[166]		✓			✓			✓
Chang 2001[179]						✓		✓
Dequeker 1998[172] SELECT, BI Study 154	✓	✓	✓	✓			✓	✓
Distel 1996[96,104]	✓	✓			✓		✓	*[b]
Furst 2002[351], BI Study 183								✓
Ghozlan 1996[352]	✓				✓			*[c]
Goei 1997[170] BI Study 044	✓	✓	✓				✓	✓
Hawkey 1998[173] MELISSA, BI Study 153	✓	✓	✓	✓			✓	✓
Hettich 1997[353] BI Study 099			✓					*[a]
Hosie 1996[168] BI Study 063	✓	✓	✓		✓		✓	✓
Hosie 1997[171] BI Study 045	✓	✓	✓		✓		✓	✓
Hsu 1999 [354], BI Study 196			✓					*[a]
Huskisson 1996[355]					✓			*[d]
Lemmel 1997[184] BI Study 035	✓		✓		✓		✓	✓
Linden 1996[169] BI Study 043	✓	✓	✓		✓		✓	✓
Lipscomb 1998[356]		✓						*[e]
Lund 1998[174] BI Study 042	✓		✓				✓	✓
Prouse 1996[357]					✓			*[d]
Reginster 1996[358]					✓			*[f]
Valat 2001[180] BI Study 094			✓			✓		✓
Wojtulewski 1996[182] BI Study 61	✓	✓	✓		✓		✓	✓
Xu 2002a [359]								✓
Xu 2002b [360]								✓
Yocum 2000[176], BI Study 181			✓			✓	✓	✓

Studies listed are those included in each review to evaluate efficacy and/or safety in patients with RA or OA. Studies in other patient populations are not listed. Reviews/meta-analyses are listed where they formed part of the analysis of efficacy and/or safety. Those referred to just in the introduction or discussion are not listed. *Studies excluded due to: [a]only abstract available, [b]pooled analysis, [c]duration of treatment less than two weeks, [d]descriptive study without control group, [e]healthy volunteer, [f]comparing different doses without other active or placebo control, [g]

Table 90: Studies with rofecoxib in patients with RA or OA included in each review

Trial (ref)	Kaplan-Machilis 1999 [114]	NICE 2000/1 [131]	Desoky 2001 [130]	Mukherjee 2001 [117]	Schnitzer 2001 [115]	Vasoo 2001 [116]	Weaver 2001 [118]	Garner 2002 Rofe [119]	Hogue 2002 [128]	Vries 2002 [123]	Rostom 2003 [126]	WMHTAC 2004
Acevedo 2001[198], Arthrotec trial, MSD Study 902		✓								✓	✓	✓
Bombardier 2000 [209] VIGOR Study		✓ + CIC		✓ +FDA 2001	✓	pre-public'n	✓	✓	✓		✓	✓
Cannon 2000[193] MSD Study 035	✓	✓			✓	✓	✓		✓		✓	✓
Day 2000[195] MSD Study 040		✓			✓	✓	✓		✓		✓	✓
Ehrich 1999[191] MSD Study 010		✓			✓		✓				✓	✓
Ehrich 2001[199] MSD Study 029		✓										✓
Geba 2001 [361], MSD Study 090				✓ 2001								✓
Geba 2002[263] VACT-1 Study		✓			✓				✓		✓	✓
Geusens 2002 [362], MSD Study 097												✓
Gibovsky 2003 [311] Pf Study 003												✓
Hawkey 2000[213] MSD Study 044 / 045		✓							✓		✓	✓
Hawkey 2003 [214] MSD Study 098 / 103												✓
Kivitz 2004[363], MSD Study 085		✓		✓ 2001								✓
Laine 1999 [192] MSD Study 044 / 045		✓			✓		✓		✓		✓	✓
Langman 1999[95]					✓	✓	✓				✓	*[a]
Lanza FL 1999[364]					✓				✓			*[b]
Lisse 2003, ADVANTAGE MSD Study 102 / 903											✓ Geba 2001	✓
McKenna 2001b[145] Pf Study 152		✓							✓		✓	✓
Moskowitz 2003 Pf Study 143												✓
Myllykangas-Luosujarvi [365] MSD Study 901												✓
Niccoli 2002 [366]												✓
Saag 2000a [197,367], MSD Study 033 MSD Study 033	✓	✓			✓		✓		✓		✓	✓
Saag 2000b [197] MSD Study 034		✓			✓						✓	✓
Schnitzer 1999[208], MSD Study 068		✓			✓		✓	✓			✓	✓
Sowers 2003, CRESCENT Pf Study 002												✓ CIC
Truitt 2001[204] MSD Study 058		✓					✓				✓	✓
Truitt 2001 [368], MSD Study 096												✓
Whelton 2001[260], SUCCESS VI, Pf Study 149		✓									✓	✓
Whelton 2002a [320], SUCCESS VII Pf Study 181												✓

Trial (ref)	Kaplan-Machilis 1999 [114]	NICE 2000/1 [131]	Desoky 2001 [130]	Mukherjee 2001 [117]	Schnitzer 2001 [115]	Vasoo 2001 [116]	Weaver 2001 [118]	Garner 2002 Rofe [119]	Hogue 2002 [128]	Vries 2002 [123]	Rostom 2003 [126]	WMHTAC 2004
Daniels , Krupa 1999 (abs)					✓		✓					
Daniels , Seidenberg 1999 (abs) review					✓							
Daniels, Gertz 1999 (abs) review					✓		✓					
Laurenzi 2000a		✓										

Studies listed are those included in each review to evaluate efficacy and/or safety in patients with RA or OA. Studies in other patient populations are not listed. Reviews/meta-analyses are listed where they formed part of the analysis of efficacy and/or safety. Those referred to just in the introduction or discussion are not listed
*Studies excluded due to: [a]pooled analysis, [b]healthy volunteer,

Table 91: Studies with valdecoxib in patients with RA or OA included in each

Trial Ref	Chavez 2003[120]	WMHTAC 2004
Bensen 2002[257] Pf Study 060	✓	✓
Fiechtner 2001 Pf Study 015	✓	✓
Kivitz 2002[254] Pf Study 053	✓	✓
Makarowski 2002 [369] Pf Study 049	✓	✓
Moskowitz 2003 Pf Study 143		✓
Pavelka 2003 [370] Pf Study 062		✓
Sikes 2002[256] Pf Study 048	✓	✓
Pf Study 016		✓ CIC
Pf Study 047		✓ CIC
Pf Study 061		✓ CIC
Pf Study 063		✓ CIC
Agrawal 2001	✓	
Goldstein 2001 (ab)	✓	
Goldstein 2002a (ab)	✓	
Goldstein 2002b (ab)	✓	

Tolerability & Safety

All but two reviews[125,129] evaluated tolerability and safety of COX-2 selective NSAIDs. Four focused on GI tolerability and safety[121-123,126] and one on cardiovascular safety.[117] Safety data, unlike efficacy data, were analysed for all patients irrespective of their disease characteristics.

Twelve studies described tolerability data [114-120,123,124,127,128,130] and 6 undertook quantitative analysis.[112,113,121,122,126,131] Table 92, pg 190, summarises the pooled estimates calculated in meta-analyses for four key endpoints. Pooled estimates as odds ratios and 95% confidence intervals were shown by two reviews;[121,131] all other meta-analyses presented summary estimates as relative risks with 95% confidence intervals.

Thirteen reviews reported the GI tolerability and safety of celecoxib,[112-117,122,123,126-128,130,131] 3 of etodolac,[123,124,131] 7 meloxicam,[114,116,121,123,124,126,131] 11 rofecoxib,[114-119,123,126,128,130,131] and 1 valdecoxib.[371] Rostom et al[126] described pooled adverse effects for celecoxib, rofecoxib and meloxicam, and for each individual agent.

Data presentation varied greatly in these reviews and three reviews indicated that overall safety of celecoxib,[114] rofecoxib[118] and meloxicam[124] was comparable to placebo.

Withdrawals due to adverse effect

Compared to placebo

Data for celecoxib (dose range 200 to 600mg daily), rofecoxib (12.5 to 25mg daily) and meloxicam (7.5mg daily), where it was reported, showed comparable withdrawal rates with placebo.[126,131] No data are available for etodolac. Some studies reported more withdrawals with higher doses of COX-2 selective NSAIDs, for example Rostom et al[126] reported a relative risk of 1.62 (95% CI 1.16 to 2.25).

Compared to non-selective NSAIDs

Celecoxib,[112] etodolac,[131] meloxicam,[114,131] and rofecoxib[119] led to significantly fewer withdrawals from adverse events than non-selective NSAIDs; COX-2 (RR 0.81 95% CI 0.73 to 0.90)[126] etodolac (0.44 95% CI 0.32 to 0.62),[131] meloxicam (OR 0.80 95% CI 0.67 to 0.96).[131]

Withdrawals due to GI adverse effects

Compared to placebo

Available data shows that COX-2 selective NSAIDs were comparable to placebo in terms of withdrawals for GI adverse effects: data for COX-2 selective agents combined;[126] celecoxib 200mg/day[131] and for rofecoxib.[119] However, one review did show an increased incidence of withdrawals for GI adverse effects with celecoxib 400mg daily compared placebo (RR 1.71 95% CI 1.03 to 2.85).[372] No data are available for etodolac or meloxicam.

Compared to non-selective NSAIDs

A majority of reviews consistently showed that COX-2 selective NSAIDs significantly reduced the incidence of GI adverse events compared with non-selective NSAIDs.[112,114-116,121,126,131] Relative risks: 0.73 (95% CI 0.69 to 0.79) for COX-2 selective NSAIDs combined;[126] 0.4 (95% CI 0.2 to 0.8) for celecoxib 400mg/day compared with ibuprofen;[131] and odds ratio 0.59 (95% CI 0.52 to 0.67) for meloxicam.[121] No significant differences were apparent on comparing etodolac with piroxicam.[131](see Table 2, pg 20)

Ulcer on endoscopy
None of the reviews evaluated endoscopic ulcers with etodolac or meloxicam.

Compared to placebo
Few comparisons of COX-2 selective NSAIDs with placebo are reported. Compared with the incidence of ulcers on endoscopy is not significantly different for COX-2 selective NSAIDs combined,[126] celecoxib,[112,115] rofecoxib[114,115,118] and valdecoxib[120]. One review[122] reported that celecoxib at 400 mg, but not 200 mg, daily significantly increased the risk of endoscopic ulcers, compared to placebo (RR 2.35 95%CI 1.02 to 5.38).

Compared to non-selective NSAIDs
Reviews consistently showed that COX-2 selective NSAIDs reduced the incidence of ulcers on endoscopy compared to non-selective NSAIDs. For selective NSAIDs combined a 73% reduction in risk was reported (RR0.27; 95% CI 0.23 to 0.32).[126] Details for individual NSAIDs are shown below.

Celecoxib
Compared with naproxen 1g and ibuprofen 2.4g daily celecoxib caused fewer endoscopic ulcers over the short term.[112,112,114-116,128,114,114,115,115,128,128] A statistically significant reduction in ulcer incidence compared to diclofenac was seen at 6 months but not 3 months.[112,114,116,128] Celecoxib (100 to 800mg daily)[112,122,126] reduced the risk of endoscopic ulcers by 70 to 80%.[112,122,126] In a stratified analysis Rostom et al[126] showed significant benefits for celecoxib compared to naproxen and ibuprofen, but not diclofenac.[126]

Rofecoxib
Significantly fewer endoscopic ulcers were reported for rofecoxib compared with ibuprofen over the short term and combined non-selective NSAIDs.[114,115,118] (RR 0.25; 95%CI 0.20 to 0.32).[126]

Valdecoxib
Limited data are available for valdecoxib:[120] after 12 weeks, valdecoxib 20mg daily had a similar incidence of gastroduodenal ulcers on endoscopy compared to naproxen 1g, ibuprofen 2.4g and diclofenac 150mg per day.

Upper GI perforations, ulcers and bleeding (PUB)
Reviews differed in their definition of PUB; for example, the HTA report for NICE defined PUBs as *'Perforations, ulcers and bleeding assessed clinically or endoscopically'*;[372] Schoenfeld as an gastric perforations, endoscopically diagnosed ulcers in patients with dyspepsia or abdominal pain and/or GI bleeding.[373]

Compared to placebo
Data are very limited and previous reports may give inaccurate estimates of risk because of incomplete study inclusions. The previous NICE HTA review found no significant differences between celecoxib and placebo (OR 1.83 95% CI0.88 to 3.83) and a significant increase in PUBs for rofecoxib versus placebo (OR 2.25 95%CI 1.12 to 4.50).

Compared to non-selective NSAIDs
Rostom et al[126] reported a 51% reduction in PUBs for COX-2 selective NSAIDs (celecoxib, rofecoxib, meloxicam) compared to non-selective NSAIDs (diclofenac, ibuprofen, naproxen or piroxicam): RR 0.49 95% CI 0.41 to 0.60. Analysis for individual non-selective NSAIDs

showed that a significant reduction in risk did not apply to diclofenac. A single trial comparing piroxicam with meloxicam did not show any difference in PUB rates.[126] Details for individual COX-2 selective agents are shown below:

Celecoxib
Celecoxib significantly reduced the risk of PUBs compared with non-selective NSAIDs[126,131] (refer to Table 5, pg 42) and preliminary analysis found that this benefit was lost when low dose aspirin was given with celecoxib.

Etodolac
Etodolac did not cause significantly fewer PUBs compared to non-selective NSAIDs in a long term RCT.[123] However the previous HTA report for NICE, which included this study, suggested significant benefits for etodolac (clinical & endoscopic PUBs OR 0.20 95% CI 0.07 to 0.53) compared with non-selective NSAIDs.

Meloxicam
Few events occurred in meloxicam trials but two reviews found no difference in the incidence of PUBs between piroxicam, diclofenac or meloxicam.[116] [114]Other studies, reporting pooled data, indicated significant benefits for meloxicam with approximately a 50% reduction in risk (refer to Table 92, pg 190); however, these reviews included studies that defined PUBs less precisely.[121,126,131]

Rofecoxib
Reviews concluded that PUBs were significantly reduced with rofecoxib compared with diclofenac, ibuprofen, nabumetone and naproxen over the short term[119] but[115,118] De Vries[123] and colleagues found, in an RCT, that over one year rofecoxib and diclofenac did not differ significantly. Pooled analyses indicated a significantly reduced risk of PUBs with rofecoxib 12.5 to 50mg/day compared to non-selective NSAIDs.[126,131](Refer to Table 92, pg 19)

Other adverse events
Renal
Abnormalities of renal function were evaluated in six reviews which found that COX-2 selective and non-selective NSAIDs had similar effects on the kidney function,[115,116,118,119] although insufficient data were available for meloxicam[114] and valdecoxib.[120]

Cardiovascular
Mukherjee and colleagues looked specifically at the cardiovascular safety of COX-2 selective NSAIDs. They reported on 4 trials: two small studies; VIGOR; and CLASS. Annualised myocardial infarction rates from VIGOR and CLASS were compared with the rate in the placebo group of a large meta-analysis of patients in primary prevention trials (0.74, 0.80 vs 0.52; $p<0.05$ for both vs placebo). There are obvious concerns about such indirect comparisons, especially as patients with RA have a higher risk of cardiovascular disease and also because of potential differences in the anti-platelet actions of non-selective NSAIDs. One review of valdecoxib found too few events to draw any conclusions.[120]

Table 92: Summary estimates presented in qualitative reviews on COX-2 selective NSAID - GI tolerabili

Drug dose /time point (where specified)	Review identifier	Comparison	Withdrawals due to AEs	95% CI	Withdrawals due to any GI AE	95% CI	Ulcer on endoscopy	95% CI			
COX 2											
COX-2 400 mg daily or less	Rostom A 2003[126]	placebo	RR 1.13	0.91 to 1.40 13 trials N=6311							
COX-2 exceeding 400 mg daily	Rostom A 2003[126]	placebo	*RR 1.62 **	*1.16 to 2.25* 6 trials N=1863							
COX-2 all doses	Rostom A 2003[126]	placebo			RR 1.35	0.83 to 2.20 8 trials n=4478	RR 1.09	0.74 to 1.60 4 trials n=2576			
COX-2 all doses	Rostom A 2003[126]	NSAID	*RR 0.81**	*0.73 to 0.90* 22 trials n=44840	*RR 0.73**	*0.69 TO 0.79* 15 trials n=49 706	*RR 0.27**	*0.23 to 0.32* 7 trials n=4677			
Celecoxib											
Celecoxib 200mg per day/ 12 weeks	Ashcroft 2001[122]	placebo					RR 1.96	0.85 to 4.55 2 trials n=953			
Celecoxib 400mg per day/ 12 weeks	Ashcroft 2001[122]	placebo					*RR 2.35**	*1.02 to 5.38* 2 trials n=941			
Celecoxib 200-600mg daily	NICE HTA 2000/1[131]	placebo	OR 0.89	0.45 to 1.77 3 trials n=2210							
Celecoxib 200mg daily/12 weeks	NICE HTA 2000/1[131]	placebo			RR 1.67	1.0 to 2.79 ? trials n=?					
Celecoxib 400mg daily/ 12 weeks	NICE HTA 2000/1[131]	placebo			*RR 1.71 **	*1.03 to 2.85* ? trials n=?					
Celecoxib 50mg per day to 800mg per day (incl 12 month CLASS data)	Rostom A 2003[126]	NSAIDs					*RR 0.28**	*0.23 to 0.35* 5 trials n=3590			

Drug dose /time point (where specified)	Review identifier	Comparison	Withdrawals due to AEs	95% CI	Withdrawals due to any GI AE	95% CI	Ulcer on endoscopy	95% CI			
Celecoxib 200-800mg daily	NICE HTA 2000/1[131]	NSAIDs	OR 0.84	0.46 to 1.52 4 trials n=10137							
Celecoxib 200mg per day/ 12 weeks	Ashcroft 2001[122]	naproxen 1000mg per day					*RR 0.22**	*0.13 to 0.37* 2 trials n=931			
Celecoxib 400mg per day/ 12 weeks	Asheroft 2001[122]	naproxen 1000mg per day					*RR 0.24 **	*0.17 to 0.33* 3 trials n=1456			
Celecoxib 400mg per day	Garner 2002 [112]	Naproxen 1000mg per day					*RR 0.2**	*0.11 to 0.38* 2 trials n= 398			
Celecoxib 400mg daily	NICE HTA 2000/1[131]	ibuprofen			*RR 0.40**	*0.20 to 0.80*					
Etodolac											
Etodolac 100-1000mg	NICE HTA 2000/1[131]	NSAID	*OR 0.44**	*0.32 to 0.62* 6 trials n=1259							
Etodolac 600mg daily 6 weeks	NICE HTA 2000/1[131]	Diclofenac 150mg daily			RR 0.89	0.31 to 2.58 2 trials n= 307					
Etodolac 600mg 8 weeks	NICE HTA 2000/1[131]	Piroxicam 20mg daily	RR 0.80	0.49 to 1.32 2 trials n=491	RR 0.74	0.41 to 1.36 2 trials n=491					
Meloxicam											
Meloxicam 7.5 to 15mg daily	NICE HTA 2000/1[131]	placebo	OR 0.84	0.45 to 1.55 2 trials n=879							
Meloxicam 7.5 to 15mg daily	Schoenfeld 1999[121]	NSAIDs			*OR 0.59 **	*0.52 to 0.67* 7 trials n=19442					
Meloxicam 7.5mg daily	Rostom A 2003[126]	NSAIDs									
Meloxicam 7.5 to 15mg	NICE HTA 2000/1[131]	NSAIDs	*OR 0.80**	*0.67 to 0.96* 8 trials n=19892							

Drug dose /time point (where specified)	Review identifier	Comparison	Withdrawals due to AEs	95% CI	Withdrawals due to any GI AE	95% CI	Ulcer on endoscopy	95% CI			
Rofecoxib											
Rofecoxib 12.5 to 50mg	NICE HTA 2000/1[131]	placebo	OR 1.74*	1.03 to 2.94 4 trials n=1861							
Rofecoxib 12.5mg 6/8 weeks	NICE HTA 2000/1[131]	placebo	RR 1.38	0.81 to 2.36 4 trials n=1527							
Rofe25mg 6/8 weeks	NICE HTA 2000/1[131]	placebo	RR 1.15	0.67 to 2.00 5 trials n= 1378							
Rofecoxib 50mg 6/8 weeks	NICE HTA 2000/1[131]	placebo	RR 1.95	0.90 to 4.26 2 trials n=571							
Rofecoxib 25mg 18/24 weeks	NICE HTA 2000/1[131]	placebo	RR 1.21	0.69 to 2.11 2 trials n=733							
Rofecoxib 50mg 18/24 weeks	NICE HTA 2000/1[131]	placebo	*RR 1.87**	*1.12 to 3.12* 2 trials n=723							
Rofecoxib 25-50mg daily	Rostom A 2003[126]	NSAIDs					RR 0.25*	0.20 to 0.32 2 trials n=1087			
Rofe 12.5 to 50mg daily	NICE HTA 2000/1[131]	NSAIDs	OR 0.81	0.54 to 1.20 3 trials n=9595							
Rofecoxib 12.5mg daily 1 year	NICE HTA 2000/1[131]	diclofenac	RR 0.68	0.36 to 1.30 2 trials n= 988	RR 0.47	0.22 to 1.02 ? trials n=?					
Rofecoxib 25mg daily 1 year	NICE HTA 2000/1[131]	diclofenac	*RR 0.70**	*0.50 to 0.97* 2 trials n= 987	RR 0.63	0.31 to 1.26 ? trials n=?					

Drug dose /time point (where specified)	Review identifier	Comparison	Withdrawals due to AEs	95% CI	Withdrawals due to any GI AE	95% CI	Ulcer on endoscopy	95% CI			
Rofecoxib 12.5mg daily 6 weeks	NICE HTA 2000/1[131]	ibuprofen	RR 0.74	0.44 to 1.27 ? trials n=?							
Rofecoxib 25mg daily 6 weeks	NICE HTA 2000/1[131]	ibuprofen	RR 0.80	0.47 to 1.36 ? trials n=?							
Rofecoxib 25mg daily 24 weeks	NICE HTA 2000/1[131]	ibuprofen	*RR 0.61**	*0.39 to 0.97* ? trials n=?							
Rofecoxib 50mg daily 24 weeks	NICE HTA 2000/1[131]	ibuprofen	RR 0.94	0.62 to 1.42 ? trials n=?							

* denotes statistical significance
AE adverse events
GI AEs Gastrointestinal adverse events
PUB perforations, ulcers and bleeds

For all quantitative reviews only comparisons where data from more than one trial are pooled is presented. Results from single trials a
Data from NICE HTA for some comparisons is limited since forest plots have been removed due to commercially sensitive status – on

Appendix 2: Search strategies

Clinical effectiveness – systematic reviews/meta-analyses

1. Cochrane Library
- Cochrane Reviews
- Database of Abstracts of Reviews of Effectiveness (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2. ARIF Database

An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3. NHSCRD (WW Web access)
- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments (WW Web access)
- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes (NCCHTA work pages: www.ncchta.org/nice/)
- Office of Technology Assessment
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Co-ordinating Office for Health Technology Assessment
- New Zealand Health Technology Assessment
- Wessex DEC Reports
- Trent Institute for Health and Related Research reports
- Agency for Healthcare Research and Quality (AHRQ)
- National Horizon Scanning Centre

5. Clinical Evidence

6. Bandolier (via the WWWeb)

7. National Research Register

8. TRIP Database

9. Drug and Therapeutics Bulletin (where appropriate)

11. Bibliographic databases
- Medline – systematic reviews
- Embase – systematic reviews
- Other specialist databases.

12. Contacts
- Cochrane Collaboration (via Cochrane Library)

- Regional experts, especially Pharmacy Prescribing Unit, Keele University (&MTRAC) and West Midlands Drug Information Service (url: www.ukmicentral.nhs.uk) for any enquiry involving drug products
- Scottish Intercollegiate Guidelines Network (SIGN). (Web page, newsletter and personal contact)
- In special circumstances, Mailbase discussion lists eg Evidence Based Medicine

Clinical effectiveness - trials

Cochrane Library (CENTRAL) Issue 4 2003
(etoricoxib OR arcoxia OR mk-663 OR mk-0663)
(valdecoxib OR bextra)
(lumiracoxib OR prexige)
(cyclooxygenase*)
(cyclo oxygenase*)
cox*
cyclo oxygenase inhibitors: ME
arthrit* OR osteoarthrit*
arthritis:ME

MEDLINE (Ovid) 1966 to October Week 5 2003
1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (39)
2 (valdecoxib or bextra).mp. (78)
3 (lumiracoxib or prexige).mp. (5)
4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6244)
5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (435)
6 (cox-2 or cox2 or cox-II or coxII).mp. (5577)
7 cyclooxygenase inhibitors/ (8907)
8 (arthrit$ or osteoarthrit$).mp. (111948)
9 exp arthritis/ (120165)
10 or/1-7 (13236)
11 or/8-9 (135062)
12 10 and 11 (1158)
13 randomized controlled trial.pt. (184388)
14 controlled clinical trial.pt. (65285)
15 randomized controlled trials/ (31418)
16 random allocation/ (49965)
17 double blind method/ (76989)
18 single blind method/ (7727)
19 or/13-18 (312525)
20 (animal not human).sh. (2727877)
21 19 not 20 (297146)
22 clinical trial.pt. (373560)
23 exp clinical trials/ (152583)
24 (clin$ adj25 trial$).ti,ab. (96466)
25 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (76132)
26 placebos/ (23379)
27 placebo$.ti,ab. (82499)
28 random$.ti,ab. (275581)
29 research design/ (38586)
30 or/22-29 (655011)
31 30 not 20 (609528)
32 31 not 21 (322306)
33 comparative study/ (1080263)
34 exp evaluation studies/ (475771)
35 follow up studies/ (276271)
36 prospective studies/ (168637)
37 (control$ or prospectiv$ or volunteer$).ti,ab. (1387557)

38 or/33-37 (2786860)
39 38 not 20 (2135191)
40 38 not (21 or 32) (2360488)
41 21 or 32 or 40 (2979940)
42 12 and 41 (530)

EMBASE (Ovid) 1980 to 2003 Week 45
1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (144)
2 (valdecoxib or bextra).mp. (250)
3 (lumiracoxib or prexige).mp. (37)
4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (5915)
5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (426)
6 (cox-2 or cox2 or cox-II or coxII).mp. (5317)
7 exp cyclooxygenase 2 inhibitor/ (7646)
8 exp cyclooxygenase 2/ (4854)
9 or/1-8 (11554)
10 (arthrit$ or osteoarthrit$).mp. (72344)
11 exp arthritis/ (88712)
12 or/10-11 (100290)
13 9 and 12 (2092)
14 randomized controlled trial/ (79774)
15 exp clinical trial/ (288658)
16 exp controlled study/ (1659851)
17 double blind procedure/ (49843)
18 randomization/ (8060)
19 placebo/ (66349)
20 single blind procedure/ (4462)
21 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (102121)
22 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (69385)
23 (placebo$ or matched communities or matched schools or matched populations).mp. (107912)
24 (comparison group$ or control group$).mp. (104120)
25 (clinical trial$ or random$).mp. (475502)
26 (quasiexperimental or quasi experimental or pseudo experimental).mp. (928)
27 matched pairs.mp. (1489)
28 or/14-27 (1998877)
29 13 and 28 (1181)

MEDLINE In-Process & Other Non-Indexed Citations (Ovid) November 11, 2003
1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (11)
2 (valdecoxib or bextra).mp. (12)
3 (lumiracoxib or prexige).mp. (5)
4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (330)
5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (25)
6 (cox-2 or cox2 or cox-II or coxII).mp. (513)
7 cyclooxygenase inhibitor$.mp. (53)
8 or/1-7 (676)
9 (arthrit$ or osteoarthrit$).mp. (1770)
10 8 and 9 (50)

Cochrane Library (CENTRAL) Issue 4 2003
(celecoxib OR celebrex OR sc-58635)
(rofecoxib OR vioxx OR mk-0966)
(etodolac OR lodine OR ultradol)
(meloxicam OR mobic)
cyclooxygenase*
(cyclo oxygenase*)
cox*
cyclooxygenase inhibitors:ME
arthrit* OR osteoarthrit*
arthritis:ME

MEDLINE (Ovid) 1966 to October Week 4 2003

1 (celecoxib or celebrex or sc-58635).mp. (977)
2 (rofecoxib or vioxx or mk-0966).mp. (721)
3 (etodolac or lodine or ultradol).mp. (311)
4 (meloxicam or mobic).mp. (402)
5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6206)
6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (429)
7 (cox-2 or cox2 or cox-II or coxII).mp. (5538)
8 cyclooxygenase inhibitors/ (8852)
9 (arthrit$ or osteoarthrit$).mp. (111520)
10 exp arthritis/ (119730)
11 or/1-8 (13748)
12 or/9-10 (134568)
13 11 and 12 (1370)
14 randomized controlled trial.pt. (181652)
15 controlled clinical trial.pt. (64404)
16 randomized controlled trials/ (30900)
17 random allocation/ (49723)
18 double blind method/ (76141)
19 single blind method/ (7650)
20 or/14-19 (308484)
21 (animal not human).sh. (2722223)
22 20 not 21 (293149)
23 clinical trial.pt. (369469)
24 exp clinical trials/ (151503)
25 (clin$ adj25 trial$).ti,ab. (95551)
26 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (75269)
27 placebos/ (23253)
28 placebo$.ti,ab. (81446)
29 random$.ti,ab. (272401)
30 research design/ (38355)
31 or/23-30 (649281)
32 31 not 21 (603924)
33 32 not 22 (320671)
34 comparative study/ (1075605)
35 exp evaluation studies/ (473284)
36 follow up studies/ (274911)
37 prospective studies/ (167162)
38 (control$ or prospectiv$ or volunteer$).ti,ab. (1380253)
39 or/34-38 (2773858)
40 39 not 21 (2123595)
41 39 not (22 or 33) (2351709)
42 22 or 33 or 41 (2965529)
43 13 and 42 (679)

EMBASE (Ovid) 1980 to 2003 Week 44

1 (celecoxib or celebrex or sc-58635).mp. (2641)
2 (rofecoxib or vioxx or mk-0966).mp. (2069)
3 (etodolac or lodine or ultradol).mp. (1075)
4 (meloxicam or mobic).mp. (1060)
5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (5872)
6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (422)
7 (cox-2 or cox2 or cox-II or coxII).mp. (5269)
8 exp Cyclooxygenase 2 Inhibitor/ (7565)
9 exp Cyclooxygenase 2/ (4819)
10 or/1-9 (12193)
11 (arthrit$ or osteoarthrit$).mp. (72193)
12 exp arthritis/ (88525)
13 or/11-12 (100085)
14 10 and 13 (2357)
15 randomized controlled trial/ (79570)

16 exp clinical trial/ (287950)
17 exp controlled study/ (1655846)
18 double blind procedure/ (49755)
19 randomization/ (7964)
20 placebo/ (66226)
21 single blind procedure/ (4448)
22 (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp. (101782)
23 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (69294)
24 (placebo$ or matched communities or matched schools or matched populations).mp. (107723)
25 (comparison group$ or control group$).mp. (103953)
26 (clinical trial$ or random$).mp. (474493)
27 (quasiexperimental or quasi experimental or pseudo experimental).mp. (927)
28 matched pairs.mp. (1489)
29 or/15-28 (1994308)
30 14 and 29 (1313)

MEDLINE In-Process & Other Non-Indexed Citations (Ovid) November 04, 2003
1 (celecoxib or celebrex or sc-58635).mp. (101)
2 (rofecoxib or vioxx or mk-0966).mp. (74)
3 (etodolac or lodine or ultradol).mp. (6)
4 (meloxicam or mobic).mp. (25)
5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (330)
6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (27)
7 (cox-2 or cox2 or cox-II or coxII).mp. (522)
8 cyclooxygenase inhibitor$.mp. (52)
9 or/1-8 (737)
10 (arthrit$ or osteoarthrit$).mp. (1757)
11 9 and 10 (61)
12 from 11 keep 1-61 (61)

Economic evaluation / decision analysis

MEDLINE (Ovid) 1966 to November Week 2 2003

1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (40)
2 (valdecoxib or bextra).mp. (81)
3 (lumiracoxib or prexige).mp. (6)
4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6313)
5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (440)
6 (cox-2 or cox2 or cox-II or coxII).mp. (5639)
7 cyclooxygenase inhibitors/ (8953)
8 (arthrit$ or osteoarthrit$).mp. (112138)
9 exp arthritis/ (120333)
10 or/1-7 (13329)
11 or/8-9 (135278)
12 10 and 11 (1165)
13 decision support techniques/ (4556)
14 markov.mp. (2552)
15 exp models economic/ (3600)
16 decision analysis.mp. (1936)
17 cost benefit analysis/ (33656)
18 or/13-17 (42517)
19 12 and 18 (21)

EMBASE (Ovid) 1980 to 2004 Week 04

1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (156)
2 (valdecoxib or bextra).mp. (284)
3 (lumiracoxib or prexige).mp. (48)
4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6202)
5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (439)
6 (cox-2 or cox2 or cox-II or coxII).mp. (5573)
7 cyclooxygenase inhibitors/ (3480)
8 (arthrit$ or osteoarthrit$).mp. (73407)
9 exp arthritis/ (93087)
10 or/1-7 (10986)
11 or/8-9 (103603)
12 10 and 11 (1387)
13 decision support techniques/ (194)
14 markov.mp. (2124)
15 exp models economic/ (8338)
16 decision analysis.mp. (1708)
17 cost benefit analysis/ (17166)
18 or/13-17 (28742)
19 10 and 18 (32)

Ovid MEDLINE In-Process & Other Non-Indexed Citations (Ovid) January 22, 2004

1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (10)
2 (valdecoxib or bextra).mp. (12)
3 (lumiracoxib or prexige).mp. (6)
4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (320)
5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (33)
6 (cox-2 or cox2 or cox-II or coxII).mp. (527)
7 cyclooxygenase inhibitor$.mp. (57)
8 or/1-7 (689)
9 markov.mp. (249)
10 model$.mp. (35510)
11 decision analysis.mp. (40)
12 cost benefit analysis.mp. (31)
13 or/9-12 (35620)
14 8 and 13 (114)

MEDLINE (Ovid) 1966 to January 2004

1 (celecoxib or celebrex or sc-58635).mp. (942)
2 (rofecoxib or vioxx or mk-0966).mp. (714)
3 (etodolac or lodine or ultradol).mp. (314)
4 (meloxicam or mobic).mp. (396)
5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (5905)
6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (422)
7 (cox-2 or cox2 or cox-II or coxII).mp. (5250)
8 cyclooxygenase inhibitors/ (8443)
9 or/1-8 (13332)
10 decision support techniques/ (4349)
11 markov.mp. (2519)
12 exp models economic/ (3561)
13 decision analysis.mp. (1854)
14 cost benefit analysis/ (31997)
15 or/10-14 (40654)
16 9 and 15 (43)

EMBASE (Ovid) 1980 to 2003 Week 47

1 (celecoxib or celebrex or sc-58635).mp. (2708)
2 (rofecoxib or vioxx or mk-0966).mp. (2118)
3 (etodolac or lodine or ultradol).mp. (1086)
4 (meloxicam or mobic).mp. (1066)
5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (5939)
6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (424)
7 (cox-2 or cox2 or cox-II or coxII).mp. (5342)
8 cyclooxygenase inhibitors/ (3412)
9 or/1-8 (13230)
10 exp arthritis/ (91818)
11 (arthrit$ or osteoarthrit$).mp. (72481)
12 or/10-11 (102255)
13 9 and 12 (2188)
14 decision support techniques/ (171)
15 markov.mp. (2076)
16 exp models economic/ (8061)
17 decision analysis.mp. (1691)
18 cost benefit analysis/ (16840)
19 or/14-18 (28072)
20 13 and 19 (23)

MEDLINE In-Process & Other Non-Indexed Citations (Ovid) January 22, 2004

1 (celecoxib or celebrex or sc-58635).mp. (120)
2 (rofecoxib or vioxx or mk-0966).mp. (79)
3 (etodolac or lodine or ultradol).mp. (6)
4 (meloxicam or mobic).mp. (24)
5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (320)
6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (33)
7 (cox-2 or cox2 or cox-II or coxII).mp. (527)
8 cyclooxygenase inhibitor$.mp. (57)
9 or/1-8 (736)
10 decision support technique$.mp. (0)
11 markov.mp. (249)
12 model$.mp. (35510)
13 decision analysis.mp. (40)
14 cost benefit analysis.mp. (31)
15 or/10-14 (35620)
16 9 and 15 (117)

Costs/Quality of life

MEDLINE (Ovid) 1966 to November Week 2 2003

1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (40)
2 (valdecoxib or bextra).mp. (81)
3 (lumiracoxib or prexige).mp. (6)
4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6313)
5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (440)
6 (cox-2 or cox2 or cox-II or coxII).mp. (5639)
7 cyclooxygenase inhibitors/ (8953)
8 (arthrit$ or osteoarthrit$).mp. (112138)
9 exp arthritis/ (120333)
10 or/1-7 (13329)
11 or/8-9 (135278)
12 10 and 11 (1165)
13 economics/ (26004)
14 exp "costs and cost analysis"/ (109788)
15 cost of illness/ (5730)
16 exp health care costs/ (21676)
17 economic value of life/ (7154)
18 exp economics medical/ (9939)
19 exp economics hospital/ (12664)
20 economics pharmaceutical/ (1296)
21 exp "fees and charges"/ (21639)
22 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (185564)
23 (expenditure$ not energy).tw. (8121)
24 (value adj1 money).tw. (338)
25 budget$.tw. (8462)
26 or/13-25 (291115)
27 12 and 26 (91)
28 from 27 keep 1-91 (91)

MEDLINE (Ovid) 1966 to January Week 2 2004

1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (40)
2 (valdecoxib or bextra).mp. (76)
3 (lumiracoxib or prexige).mp. (7)
4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (5905)
5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (422)
6 (cox-2 or cox2 or cox-II or coxII).mp. (5250)
7 cyclooxygenase inhibitors/ (8443)
8 or/1-7 (12738)
9 quality of life/ (38784)
10 life style/ (18785)
11 health status/ (22462)
12 health status indicators/ (7852)
13 value of life/ (4175)
14 quality of wellbeing.tw. (2)
15 or/9-14 (84063)
16 8 and 15 (30)

EMBASE (Ovid) 1980 to 2004 Week 04

1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (156)
2 (valdecoxib or bextra).mp. (284)
3 (lumiracoxib or prexige).mp. (48)
4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6202)
5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (439)
6 (cox-2 or cox2 or cox-II or coxII).mp. (5573)
7 cyclooxygenase inhibitors/ (3480)
8 (arthrit$ or osteoarthrit$).mp. (73407)

9 exp arthritis/ (93087)
10 or/1-7 (10986)
11 or/8-9 (103603)
12 10 and 11 (1387)
13 cost benefit analysis/ (17166)
14 cost effectiveness analysis/ (31987)
15 cost minimization analysis/ (607)
16 cost utility analysis/ (964)
17 economic evaluation/ (1725)
18 (cost or costs or costed or costly or costing).tw. (108193)
19 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (50882)
20 (technology adj assessment$).tw. (1029)
21 or/13-20 (161562)
22 10 and 21 (225)
23 11 and 22 (115)
24 exp quality of life/ (43795)
25 life style/ (14808)
26 health status/ (19424)
27 quality of wellbeing.mp. (5)
28 or/24-27 (73456)
29 12 and 28 (41)
30 23 or 29 (143)

MEDLINE In-Process & Other Non-Indexed Citations (Ovid) January 22, 2004
1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (10)
2 (valdecoxib or bextra).mp. (12)
3 (lumiracoxib or prexige).mp. (6)
4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (320)
5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (33)
6 (cox-2 or cox2 or cox-II or coxII).mp. (527)
7 cyclooxygenase inhibitor$.mp. (57)
8 or/1-7 (689)
9 (economic$ or cost or costs or costly or costing or price or pricing or pharmacoeconomics).mp. (6456)
10 (expenditure$ not energy).mp. [mp=title, abstract] (216)
11 (value adj1 money).mp. (15)
12 budget$.mp. (293)
13 or/9-12 (6778)
14 8 and 13 (11)
15 quality of life.mp. (1953)
16 life style.mp. (103)
17 health status.mp. (408)
18 value of life.mp. (6)
19 quality of wellbeing.mp. (0)
20 or/15-19 (2405)
21 8 and 20 (7)
22 14 or 21 (17)

Cochrane Library Issue 4 2003

See search strategy for effectiveness above.

MEDLINE (Ovid) 1966 to November Week 2 2003
1 (celecoxib or celebrex or sc-58635).mp. (1003)
2 (rofecoxib or vioxx or mk-0966).mp. (751)
3 (etodolac or lodine or ultradol).mp. (312)
4 (meloxicam or mobic).mp. (408)
5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (440)
6 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6313)
7 (cox-2 or cox2 or cox-II or coxII).mp. (5639)
8 cyclooxygenase inhibitors/ (8953)
9 exp arthritis/ (120333)

10 or/1-8 (13924)
11 9 and 10 (1115)
12 economics/ (26004)
13 exp "costs and cost analysis"/ (109788)
14 cost of illness/ (5730)
15 exp health care costs/ (21676)
16 economic value of life/ (7154)
17 exp economics medical/ (9939)
18 exp economics hospital/ (12664)
19 economics pharmaceutical/ (1296)
20 exp "fees and charges"/ (21639)
21 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (185564)
22 (expenditure$ not energy).tw. (8121)
23 (value adj1 money).tw. (338)
24 budget$.tw. (8462)
25 or/12-24 (291115)
26 11 and 25 (88)
27 from 26 keep 1-88 (88)

MEDLINE (Ovid) 1966 to January Week 2 2004
1 (celecoxib or celebrex or sc-58635).mp. (942)
2 (rofecoxib or vioxx or mk-0966).mp. (714)
3 (etodolac or lodine or ultradol).mp. (314)
4 (meloxicam or mobic).mp. (396)
5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (5905)
6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (422)
7 (cox-2 or cox2 or cox-II or coxII).mp. (5250)
8 cyclooxygenase inhibitors/ (8443)
9 or/1-8 (13332)
10 quality of life/ (38784)
11 life style/ (18785)
12 health status/ (22462)
13 health status indicators/ (7852)
14 value of life/ (4175)
15 quality of wellbeing.tw. (2)
16 or/10-15 (84063)
17 9 and 16 (35)

EMBASE (Ovid) 1980 to 2004 Week 04
1 (celecoxib or celebrex or sc-58635).mp. (2864)
2 (rofecoxib or vioxx or mk-0966).mp. (2253)
3 (etodolac or lodine or ultradol).mp. (1102)
4 (meloxicam or mobic).mp. (1099)
5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6202)
6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (439)
7 (cox-2 or cox2 or cox-II or coxII).mp. (5573)
8 exp Cyclooxygenase 2 Inhibitor/ (8059)
9 exp Cyclooxygenase 2/ (5102)
10 or/1-9 (12921)
11 (arthrit$ or osteoarthrit$).mp. (73407)
12 exp arthritis/ (93087)
13 or/11-12 (103603)
14 cost benefit analysis/ (17166)
15 cost effectiveness analysis/ (31987)
16 cost minimization analysis/ (607)
17 cost utility analysis/ (964)
18 economic evaluation/ (1725)
19 (cost or costs or costed or costly or costing).tw. (108193)
20 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (50882)
21 (technology adj assessment$).tw. (1029)

22 or/14-21 (161562)
23 10 and 22 (445)
24 13 and 23 (204)
25 exp quality of life/ (43795)
26 life style/ (14808)
27 health status/ (19424)
28 quality of wellbeing.mp. (5)
29 or/25-28 (73456)
30 10 and 13 and 29 (104)
31 24 or 30 (281)

MEDLINE(Ovid) In-Process & Other Non-Indexed Citations January 22, 2004

1 (celecoxib or celebrex or sc-58635).mp. (120)
2 (rofecoxib or vioxx or mk-0966).mp. (79)
3 (etodolac or lodine or ultradol).mp. (6)
4 (meloxicam or mobic).mp. (24)
5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (320)
6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (33)
7 (cox-2 or cox2 or cox-II or coxII).mp. (527)
8 cyclooxygenase inhibitor$.mp. (57)
9 or/1-8 (736)
10 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconmic$).mp. (6615)
11 (expenditure$ not energy).mp. (216)
12 (value adj1 money).mp. (15)
13 budget$.mp. (293)
14 or/10-13 (6937)
15 9 and 14 (13)
16 quality of life.mp. (1953)
17 life style.mp. (103)
18 health status.mp. (408)
19 value of life.mp. (6)
20 quality of wellbeing.mp. (0)
21 or/16-20 (2405)
22 8 and 21 (0)
23 from 15 keep 1-13 (13)

Quality of life of arthritis

MEDLINE(Ovid)1966 to January Week 1 2004
1 exp arthritis/ (118554)
2 quality of life/ (38688)
3 life style/ (18766)
4 health status/ (22407)
5 health status indicators/ (7839)
6 value of life/ (4175)
7 quality of wellbeing.tw. (2)
8 or/2-7 (83896)
9 (meta-analysis or review literature).sh. (5839)
10 metaanal$.tw. (381)
11 meta-analy$.tw. (10064)
12 (systematic$ adj4 (review$ or overview$)).tw. (6090)
13 meta-analysis.pt. (8408)
14 review.pt. (990033)
15 case report.sh. (0)
16 letter.pt. (492568)
17 historical article.pt. (205338)
18 review of reported cases.pt. (48354)
19 review multicase.pt. (7866)
20 review.ti. (109665)
21 review literature.pt. (35109)
22 9 or 10 or 11 or 12 or 13 or 14 or 20 or 21 (1050467)
23 15 or 16 or 17 or 18 or 19 (748610)
24 22 not 23 (984099)
25 animals/ (3494785)
26 human.sh. (8239392)
27 25 not (25 and 26) (2705690)
28 24 not 27 (895681)
29 8 and 28 (11593)
30 1 and 29 (189)

Appendix 3: Rationale for data analysis approach to clinical effectiveness evidence

In order to generate a single estimate for each COX-2 selective NSAID for each decision analytic model, there was an opportunity to pool results within each COX-2 trials across a number of drug doses, across a range of follow up durations, across trials of varying methodological quality, across a number of comparator conventional NSAIDs and across OA and RA indications. In order to test to acceptability of this approach to pooling an initial investigation using one of the COX-2 selective NSAIDs (Celecoxib) across a range of outcomes where a number of trials were available (i.e. VAS pain, withdrawal due to lack of efficacy, withdrawal due to GI-specific adverse events and level of myocardial infarctions).

Heterogeneity was examined by univariate and multivariate meta-regression using study quality (Jadad score), type of arthritis, choice of convention NSAID and follow up as covariates. In addition to assess the effect of COX-2 dose, results were stratified by drug dose.

As can be seen from the tables below although there was some tendency for outcome to vary across COX-2 dose there was no evidence of significant statistical heterogeneity in this or the other covariates across the various outcomes examined. In view of this, it was concluded that it was acceptable to pool trials within each COX-2 selective NSAID across COX-2 dose, across type of NSAID, across follow up and across OA/RA. However, in addition to an overall pooled outcome result, results are also presented in the report stratified by COX-2 dose and for OA and RA seperately.

VAS pain - all NSAID vs all celecoxib doses		
	Mean difference (95% CI)	
Celecoxib 200mg/d	-1.4 (-4.8 to 2.0)	
Celecoxib 400mg/d	2.3 (-2.2 to 6.8)	
Celecoxib >400mg/d	-0.8 (-2.0 to 0.4)	
Meta-regression	**Univariate**	**Multivariate**
Jaded	0.650	0.477
OA/RA	0.130	0.101
NSAID	0.533	0.907
Follow up	0.40	0.229
Withdrawal due to lack of efficacy – all NSAID vs all celecoxib doses		
	Relative risk (95% CI) [N trials]	
Celecoxib 200mg/d	1.02 (0.86 to 1.21)	
Celecoxib 400mg/d	1.02 (0.89 to 1.16)	
Celecoxib >400mg/d	0.89 (0.74 to 1.07)	
Meta-regression	**Univariate**	**Multivariate**
Jaded	0.106	0.153
OA/RA	0.615	0.660
NSAID	0.267	0.198
Follow up	0.644	0.499

GI withdrawals - all NSAID vs all celecoxib doses		
	Relative risk (95% CI) N trials]	
Celecoxib 200mg/d	*0.44 (0.35 to 0.56) [10]*	
Celecoxib 400mg/d	*0.42 (0.30 to 0.57) [6]*	
Celecoxib >400mg/d	*0.50 (0.39 to 0.65) [6]*	
Meta-regression	**Univariate**	**Multivariate**
Jaded	0.260	0.823
OA/RA	0.177	0.173
NSAID	0.250	0.143
Follow up	0.528	0.516
MI - all NSAID vs all celecoxib doses		
	Relative risk (95% CI) [N trials]	
Celecoxib 200mg/d	4.48 (0.83 to 24.1) [2]	
Celecoxib 400mg/d	*2.87 (1.02 to 8.06) [7]*	
Celecoxib >400mg/d	2.19 (0.38 to 12.5) [3]	
Meta-regression	**Univariate**	**Multivariate**
Jaded	0.922	0.939
OA/RA	0.827	0.830
NSAID	0.664	0.847
Follow up	0.731	0.967

Appendix 4: Citations of excluded studies

Code	Reasons for exlcusion	References excluded
A	Duration less than two weeks	328,352,374-377
B	Controlled trials without randomisation/observational studies with a control group	378-383
C	Observational studies without a control group	357,384-391
D	Non-OA/RA patients	392,393
E	Health volunteers	394-397
F	Trials with no relevant outcomes reported	398-405
G	Systematic reviews with no relevant outcomes reported	406-414
H	Interim trial reports	218,341,342,346,415
I	RCTs with no active/placebo comparators	358,374,416-419
J	Only abstract available	420,421
K	Letters, editorials, comments, news without additional trial data	422-426
L	Not intervention of interest	427-431
M	Pooled analysis with no search strategy	79-86 87-94 95-101,432 102-108 109
N	Narrative review with no search strategy	433-439
O	Sub-therapeutic doses and dose titrating studies	324,329,332,339,344,348,350,440 326,330,333,337,441-443 325,335,336,444
Z	Others	349,445-449

Appendix 5: Details of characteristics of included randomised controlled trials

Celecoxib

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Simon (1998) [138] USA 2-weeks Pfizer Study 013	Celecoxib 80mg per day (40mg bd) Celecoxib 200mg per day (100mg bd) Celecoxib 400mg per day (200mg bd) Placebo	71 73 76 73	61 61 63 62	65 65 75 73	9.3 9.8 9.0 11.7	NR NR NR NR	NR* NR* NR* NR*	NR** NR** NR** NR**	
Bensen (1999) [139,140] [141] USA 97 centres 12-weeks Pfizer Study 020 Also Zhou et al (1999)	Placebo Celecoxib 100mg per day (50mg bd) Celecoxib 200mg per day (100mg bd) Celecoxib 400mg per day (200mg bd) Naproxen 1000mg per day (500mg bd)	220 218 217 222 216	62 62 63 62 62	69 73 72 71 75	9 10 9 10 11	NR NR NR NR NR	10 9 12 10 7	NR NR NR NR NR	
Williams (2000) [142] USA 50 centres 6-weeks Pfizer Study 060	Celecoxib 200mg per day (100mg bd) Celecoxib 400mg per day (200mg bd) Placebo	231 223 232	63.0 62.7 62.6	66 67 67	8.6 9.3 8.8	NR NR NR	NR* NR* NR*	11-23%** 11-23%** 11-23%**	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Goldstein (2001b)[143] USA 1142 centres 37 countries 12-weeks SUCCESS-1 Pfizer Study 096 (Pfizer 2004 submission)	Celecoxib 200mg per day (100mg bd) Celecoxib 400mg per day (200mg bd) Diclofenac^ 100mg per day (50mg bd) Naproxen^ 100mg per day (500mg bd)	4421 44293 510 914	62.6 62.4 64.6	74 73 74	7.8 7.8 7.8	NR* NR NR	84** 42*** 	7.4 8.2 7.4^^	
Kivitz (2001)[144] USA & Canada 176 centres 12-weeks Pfizer Study 054	Celecoxib 200mg per day (100mg bd) Celecoxib 400mg per day (200mg bd) Celecoxib 800mg per day (400mg bd) Naproxen 2000mg per day (1000mg bd) Placebo	216 207 213 207 218	62 62 61 64 64	65 65 67 66 67	7.3 7.2 6.9 7.3 7.9	NR NR NR NR NR	NR NR NR NR NR	NR NR NR NR NR	
McKenna (2001b)[145] USA 20 centres 6-weeks Pfizer Study 152	Celecoxib 200mg qd Rofecoxib 25mg qd Placebo	63 59 60	62 61.5 63	67 71 75	11.2 10.1 11.5	71 81 83	51 56 67	NR NR NR	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
McKenna (2001a)[146]	Celecoxib 200mg per day (100mg bd)	199	62	68	8.4	77.6	4	NR	
		200	63	62	8.5	78.4	3	NR	
UK	Diclofenac 150mg per day (50mg tds)	201	60	66	8.8	77.5	4.5	NR	
6-weeks									
Pfizer Study 118	Placebo								
Pfizer Study 021	Placebo	242	61	69	9.6	NR	9	NR	
	Celecoxib								
US & Canada	100mg per day (50mg bd)	252	61	65	8.8	NR	6	NR	
80 centres	200mg per day (100mg bd)	239	62	68	9.0	NR	9	NR	
12-weeks	400mg per day (200mg bd)	233	61	70	9.1	NR	3	NR	
(Pfizer 2000 submission)	Naproxen 1000mg per day (500mg bd)	226	62	68	9.2	NR	3	NR	
McKenna (2002)[147]	Celccoxib 200mg per day (100mg bd)	346	63.3	71	7.3	5.5%	2.6%	7.8%	
		341	64.1	72	6.6	5.0%	2.6%	8.8%	
Multicentre	Diclofenac 100mg per day (50mg bd)								
6-weeks									
Pfizer Study 042									
Pfizer Study 047	Placebo	101	63.1	70	9.1	NR	14	Not reported	
USA	Celecoxib 50mg per day (25mg bd)	101	64.0	76	8.6	NR	13		
26 centres	Celecoxib 200mg per day (100mg bd)	101	63.5	70	9.4	NR	9		
4-weeks	Celecoxib 800mg per day (400mg bd)	99	62.1	70	9.9	NR	6		
(Pfizer 2000 submission)									

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Whelton (2002) [260,450] SUCCESS VI US and Canada (101 centres) 6 weeks Pfizer Study 149	Celecoxib 200mg per day (200mg od) Rofecoxib 25mg per day (25mg od)	411 399	74.0 74.1	66.5% 66.4%	13.6 11.7	NR NR	NR NR	NR NR	
Williams (2001) [148] USA 6 weeks Pfizer Study 087	Celecoxib 200mg per day (100mg bd) Celecoxib 400mg qd Placebo	243 231 244	62 61 61	69 69 73	9.5 9.4 9.7	NR NR NR	NR NR NR	NR NR NR	
Suarez-Otero (2002) [149] Mexico 6-weeks	Celecoxib 200mg per day (100mg bd) Diclofenac-cholestryamine 280mg per day (140mg bd)	40 41	56 59	NR NR	3.2 3.4	NR NR	NR NR	NR NR	
Whelton A (2002a) [261] SUCCESS VII 115 centres US & Canada. 6 weeks. Pfizer Study 181	Celecoxib 200mg per day (200 mg od) Rofecoxib 25mg per day (25 mg od)	549 543	73.3 73.1	63.9 60.1	11.7 10.1	NR NR	NR NR	NR NR	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Gibofsky (2003)[150] US and Canada 6 weeks Pfizer Study 003	Celecoxib 200mg per day (200mg od) Rofecoxib 25mg per day (25mg od) Placebo	189 190 96	62.2 63.4 63.1	69 66 65	6 5 6	8.6 8.8 8.3	-	NR NR NR	
Hawel 2003[151] Austria 2-weeks (15-days)	Dexibupofen 800mg per day (400mg bd) Celecoxib 200mg per day (100mg bd)	74 74	NR NR	55 43	NR NR	NR NR	NR NR	NR NR	
Pincus 2004a[152,153] USA 6 weeks PACESa Pfizer Study 010	Celecoxib 200mg per day (200mg od) Acetaminophen 4g per day (1000mg qds) Placebo	181 171 172	64.5* 63.6* 62.6*	61 62 64	9.5 9.7 9.3	NR NR NR	NR NR NR	NR NR NR	
Sowers 2002 CRESCENT, Pfizer Study 002, 65 Centres North America, Europe & Chile 12 weeks (Pfizer 2004 submission)	Celecoxib 200mg per day (200mg od) Rofecoxib 25 mg per day (25 mg od) Naproxen 1000mg per day (500mg bd)	136 138 130	61 62 64	62 59 60	NR NR NR	NR NR NR	NR NR NR	NR NR NR	

Author/trial name (year) Country Duration[a]	**Intervention & comparator[b]**	**N[c]**	**Age (years)[d]**	**% female**	**Disease duration (years)[d]**	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Pincus 2004b [152] USA 6 weeks PACESb Pfizer Study 249	Celecoxib 200mg per day (200mg od) Acetaminophen 1000mg qds Placebo	189 185 182	63.5* 63.6* 62.6*	67 63 64	9.3 9.9 8.7	NR NR NR	NR NR NR	NR NR NR	
Simon 1998b [138] USA 4-weeks Pfizer Study 012	Celecoxib 80mg per day (40mg bd) 400mg per day (200mg bd) 800mg per day (400mg bd) Placebo	 81 82 82 85	 55.6 55.5 56.7 56.5	 67 89 79 75	 9.7 10.9 10.5 12.8	 NR NR NR NR	 NR* NR* NR* NR*	 NR** NR** NR** NR**	
Emery 1999 [154] Multicentre Worldwide 132 centres 24-weeks Pfizer Study 041	Celecoxib 400mg per day (200mg bd) Diclofenac 150mg per day (75mg bd)	326 329	56 55	76 71	11.0 9.9	9+ 8	NR NR	0 0	
Simon 1999 [155,156] 79 centres USA & Canada 3-months Pfizer Study 022	Celecoxib 200mg per day (100mg bd) Celecoxib 400mg per day (200mg bd) Celecoxib 800mg per day (400mg bd) Naproxen 1000mg per day (500mg bd) Placebo	240 235 218 500 231	54 55 54 55 54	74 73 78 79 77	11 11 10 10 11	NR NR NR NR NR	43 38 30 33 31	10 11 6 8 8	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Pfizer 023 (1998) USA & Canada 104 centres 12 weeks (Pfizer 2000 submission)	Placebo Celecoxib 400mg per day (200mg bd) Celecoxib 800mg per day (400mg bd) Naproxen 1000mg per day (500mg bd)	221 228 218 217	54 56 54 54	76 74 72 72	9.7 10.7 9.8 10.3	NR NR NR NR	8 9 6 6	NR NR NR NR	
Silverstein 2000 [157,158 159,160 161,162 163] CLASS study, US & Canada, multicentre.¶ ≥ 26 weeks Pfizer Study 035/102	Celecoxib 800mg per day (800 mg od) Diclofenac 150mg per day (150 mg od) Ibuprofen 2400mg per day (2400mg od)	3987 (27.2 % RA) 1996 (27% RA) 1985 (27.6 % RA)	60.6 60.1 59.5	68.6 67.4 70.8	OA > 10, RA >11 OA 10.4 RA 10.5 OA 9.9 RA 10.9	Not clear*	8.4 8.5 7.6	20.9 21.5 19.3	

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Goldstein (2001)[164] USA 75-centres 3-months Pfizer Study 062	Celecoxib 400mg per day (200mg bd) Naproxen 1000mg per day (500mg bd)	270 267	57 58	67 67	9.5/11.6 11.0/8.9	Not stated	7.8 7.5	Not stated*	
Pfizer 071 (1998) USA 121centres 12 weeks (Pfizer 2000 submission)	Celecoxib 400mg per day (200mg bd) Diclofenac 150mg per day (75mg bd) Ibuprofen 2400mg per day (800mg tds)	366 387 346	57 57 58	70 67 66	10.0/8.8 11.0/10.7 10.4/10.1	NR NR NR	11 12 12	NR NR NR	
Chan 2002[165] Hong Kong 6-months	Celecoxib 400mg per day (200mg bd) + placebo Diclofenac 150mg per day (75mg bd) + omeprazole 20mg per day (20mg od)	144 143	67 69	39 35	NR NR	NR NR	20.8+ 23.1	6.2 12.6	
Pfizer 105 (2000) China 14 centres 12 weeks (Pfizer 2004 submission)	Celecoxib 200mg per day (100mg bd) Diclofenac 100mg per day (50mg bd)	332 334	50 49	86 82	NR NR	56% 57%	0 1	NR NR	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Pfizer 106 (2000) Taiwan 6 centres 12 weeks (Pfizer 2004 submission)	Celecoxib 200mg per day (100mg bd) Diclofenac 100mg per day (50mg bd)	63 62	56 53	84 82	NR NR	82 83	5 13	NR NR	
Pfizer 107 (2000) Hong Kong 4 centres 12 weeks (Pfizer 2004 submission)	Celecoxib 200mg per day (100mg bd) Diclofenac 100mg per day (50mg bd)	45 44	53 53	87 77	NR NR	82 86	7 14	NR NR	
Pfizer 209 (2003) International multicentre 6 weeks (Pfizer 2004 submission)	Celecoxib 200mg per day (200mg od) Naproxen 1000mg per day (500mg bd) Placebo	127 128 67	58 58 58	80 82 76	5.4 5.1 6.2	NR NR NR	NR NR NR	NR NR NR	
Pfizer 211 (2003) USA 31 centres 6 weeks (Pfizer 2004 submission)	Celecoxib 200mg per day (200mg od) Naproxen 1000mg per day (500mg bd) Placebo	127 129 67	59.6 60.5 61.7	72 64 60	5.3 6.4 6.6	NR NR NR	NR NR NR	NR NR NR	

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Pfizer 210 (2003) USA	Celecoxib 200mg per day (200mg od)	145	65.9	67	5.3	NR	NR	NR	
24 centres 6 weeks (Pfizer 2004 submission)	Naproxen 1000mg per day (500mg bd)	144	64.1	68	6.4	NR	NR	NR	
	Placebo	78	63.9	67	6.6	NR	NR	NR	
Pfizer 216 (2002) Japan	Celecoxib 200mg per day (100mg bd)	382	62	68	NR	NR	NR	NR	
85 centres 4 weeks (Pfizer 2004 submission)	Loxoprofen 180mg per day (60mg tds)	385	63	67	NR	NR	NR	NR	
	Placebo	192	63	63	NR	NR	NR	NR	

[a]Duration of follow-up [b]Dose per day [c]Number of randomised [d]Values are means unless otherwise specified
*S=steroid/A=aspirin/Ac=anticoagulant/GPA=gastroprotective agent

Etodolac

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Bacon 1990a Overview Efficacy of Etodolac [217,218] 6 wks	Etodolac 600mg per day (300mg bd) Naproxen 1000mg per day (500mg bd)	70 73	59.8 61.7	78 79	NR NR	All NSAIDs incl aspirin withdrawn up to 14d prior	Pts excl if hx of GI disease / GI haemorrhage within last 5y	Excluded All NSAIDs incl aspirin withdrawn up to 14d prior	
Bacon 1990b Overview Efficacy of Etodolac [217,218] 12 wks	Etodolac 600mg per day (300mg bd) Piroxicam 20mg per day (20mg od)	170 165	59.5 58.1	77 75	NR NR	All NSAIDs incl aspirin withdrawn up to 14d prior	Pts excl if hx of GI disease / GI haemorrhage within last 5y	Excluded All NSAIDs incl aspirin withdrawn up to 14d prior	
Bacon 1990c Overview Efficacy of Etodolac [217,218] 8 wks	Etodolac 600mg per day (200mg tds) Diclofenac 150mg per day (50mg tds)	98 106	59.0 59.1 	78 77	NR NR	All NSAIDs incl aspirin withdrawn up to 14d prior	Ps excl if hx of GI disease / GI haemorrhage within last 5y	Excluded All NSAIDs incl aspirin withdrawn up to 14d prior	
Williams 1989 [219] UK 4 weeks	(Knee) Etodolac 600mg per day (300 mg bd) Placebo (Hip) Etodolac 600mg per day (300 mg bd) Placebo	50 54 54 52	62.9 62.7 61.3 64.0	64 59 48 50	5.1 5.2 4.7 4.2	N/A N/A	- -	- -	
Freitas 1990 [220] Brazil 8 weeks	Etodolac 600mg per day (300 mg bd) Piroxicam 20mg per day (20mg od)	33 32	53 50	97 81	N/A	100? 100?	-	-	

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Brasseur 1991 [221] Belgium 6 weeks	Etodolac 600mg per day (300 mg bd) Diclofenac SR 100mg per day (100mg od)	32 29	63.3 60.2	81 69	N/A N/A	N/A N/A	-	-	
Karbowski 1991 [222] Country NR; prob Germany 6 weeks	Etodolac 600mg per day (300mg bd) Indomethacin 150mg per day (50mg tds)	31 33	53.5 53.8	61% 61%	NR	Allowed % not given	CT	CT	
Palferman 1991 [223] UK 6 weeks	Etodolac 600mg per day (300 mg bd) Naproxen 1000mg per day (500 mg bd)	29 27	61.6 64.5	59 67	N/a N/a	100 100	-	-	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Paulsen 1991 [224] Country NR; but likely to be Chile/Argentina /Portugal/brazil 8 weeks	Etodolac 600mg per day (300 mg bd) Piroxicam 20mg per day (20mg od)	112 108	58 58	78% 77%	NR	Allowed but % not reported	CT	CT	
Pena 1991 [225] Colombia 8 weeks	Etodolac 600mg per day (300 mg bd) Naproxen 1000mg per day (500 mg bd)	31 31	62.7 62.3	84 90	N/a N/a	100 100	-	-	
Perpignano 1991 [226] Italy 4 weeks	Etodolac 600mg per day (600mg od) Naproxen 750mg per day (750mg od)	20 (10 each group)	51.9 (SD 12.8) ET group, 55.7 (SD 8.8) NAP group Overall range 39 to 65	11/20 (55%)	Patients in acute phase requiring NSAIDS (acute phase defined by presence of at least 3 symptoms); no other details	No details (though states that patients underwent 7 day washout period)	Not stated, but patients excluded with peptic ulcer or who had an endoscopic score equal to or above 2 (0-5 scale from normal mucosa=0 to frank ulcer=5)	No details	
Dick WC 1992 [227] Europe 6 weeks	Etodolac 600mg per day (300 mg bd) Piroxicam 20mg per day (20mg od)	57 59	59.5 57.3	72% 64%	CT	Response required as inclusion criterion	No details	No details	

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Grisanti 1992 [228] Country NR 8 weeks	Etodolac 600mg per day (600mg od) Diclofenac 150mg per day (150mg od)	85 87	59 59	86% 86%	NR	Allowed but % not reportd	Peptic ulcer of GI bleed in the previous 5 years excluded.	NR	
Waterworth 1992 [229] Country not specified, but both authors from New Zealand. 6 weeks	Etodolac 600mg per day (300mg bd) Piroxicam 20mg per day (20mg od)	28 29	59.8 59.3	43% 69%	NR	CT	CT	CT	
Burssens 1993 [230] Europe 4 weeks	Etodolac SR 600mg per day (600mg od) Tenoxicam 20mg per day (20mg od)	37 36	64 59	62% 64%	CT	Response required as inclusion criterion	Not stated, but patients with active peptic ulcer or a history of peptic ulcer or gi haemorrhage excluded	Not stated	
Eisenkolb 1993 [231] Europe 6 weeks	Etodolac 600mg per day (600mg od) Diclofinac 150mg per da7y (150mg od)	66 69	61.4 60.5	65% 65%	CT	Response required as inclusion criterion	-	-	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Chikanza 1994 [232] 3 centres in UK 8 weeks (but 4 weeks for eto; and 4 weeks for naprox)	Etodolac (E) 600mg per day (300mg bd) Naproxen (N)1000mg per day (500mg bd) E-N N-E	 39 37	 61 63	 9:30 8:29	NR	NR	NR	NR	
Lucker 1994 [233] Germany 3 months	Nimesulide 200mg per day (200mg od) Etodolac 600mg per day (600mg od)	100 99	65.0 63.7	68% 66%	NR	Use of NSAIDs a requirement for entry into trial.	NR	NR	
Perpignano 1994 [234] Italy 8 weeks	EtodolacSR 600mg per day (600mg od) Tenoxicam 20mg per day (20mg od)	60 60	70.4 71.0	85% 92%	NR	% not given	Anyone with a <3yr history or GI ulcer/haemorrhage excluded	NO	
Dore 1995 [235] Country not stated; probably USA (11 centres) 4 weeks	Etodolac 800mg per day (400mg bd) Naproxen 1000mg per day (500mg bd) Placebo bd	86 82 86	63.8 63.7 63.6	60% 63% 65%	NR	Allowed but % not given.	Excluded.	5% 10% 13%	

Author/trial name (year) Country Duration[a]	**Intervention & comparator[b]**	**N[c]**	**Age (years)[d]**	**% female**	**Disease duration (years)[d]**	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Schnitzer 1995 [236] Country NR, probably USA 4 weeks	Etodolac 800mg per day (400mg bd) Nabumetone 1500mg per day (1500mg od) Placebo	91 89 90	63.81 62.38 65.26	70.3% 69.7% 65.6%	NR	Allowed % not reported	Major GI bleeding excluded	Allowed	
Jennings 1997 [237] US 5 weeks	Etodolac 800mg per day (400 mg bd) Naproxen 1000mg per day (500 mg bd)	29 31	45.0 50.8	75.9 74.2	N/A	N/A	-	-	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Rogind 1997 [238] Denmark (19 centres) 8 weeks	Etodolac 600mg per day (300mg bd) Piroxicam 20mg per day (20mg od)	138 133	67.0 67.5	79.7% 77.4%	NR NR	NR NR	Not stated, but patients with history of gi bleeding or gastric ulcer were excluded	Treatment with other kinds of anti-inflammatory drugs NOT allowed.	
Schnitzer 1997 [239] USA, 4 weeks NB reports on three trials, only trial 1 extracted (2 and 3 reported elsewhere and already extracted)	Etodolac 1600mg per day (400 mg qds) Etodolac 800mg per day (200 mg qds) Naproxen 1000mg per day (500 mg bd) Placebo	N=424	Et-400 arm: 62.6 (SD 9.6); Et-200 arm: 65.2 (SD 9.3); Nap arm: 62.2 (SD 10.2); Placebo arm: 63.8 (SD 9.0)	75% (n=320)	Not stated	Some patients previously on long-acting NSAIDS, but number not stated	Patients with history of GI bleeding or ulcers excluded	≤325mg/d aspirin permitted; number of patients not stated	

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Taha 1989 [240,241] UK, single centre, 4 weeks	Etodolac 600mg per day (300mg bd) Naproxen 1000mg per day (500mg bd)	15^ 15^	50 57	73.3 66.7	11 6	80 80	NR NR	NR NR	
Delcambre, 1990, France [207] 14 centres, 6 weeks	Etodolac 600mg per day (200mg tds) Indomethacin (100mg per day (25mg bd and 50mg od)	50 52	56.5 56.8	17.3% (based on 98 patients: 17 female, 81 male, 4 missing values)	9.0 7.5	Not reported	No details	No details	
Taha 1990 [241,242] UK, single centre, 4 weeks	Etodolac 600mg per day (300mg bd) Naproxen 1000mg per day (500mg bd)	14^ 13^	50 60	71.4 69.2	NR NR	78.6% 76.9%	0 0 (excluded)	Can't tell	
Lightfoot 1997 [243] USA & Europe 12 weeks	Etodolac 400mg per day (200 mg bd) Etodolac 600mg per day (300 mg bd) Piroxicam 20 mg qd	140 * 147 * 139 *	57 58 56	75% 60% 69%	> 6 months	Response required as inclusion criterion	NR	NR	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Neustadt 1997 [244] USA 3 years	Etodolac 300mg per day (150 mg bd) Etodolac 1000mg per day (500 mg bd) Ibuprofen 600 mg qd	620 409 417	53.2 53.0 53.1	71% 69% 72	3.6 3.5 3.6	Response required as inclusion criterion	Can't tell	Can't tell	

[a]Duration of follow-up [b]Dose per day [c]Number of randomised [d]Values are means unless otherwise specified
[e]S=steroid/A=aspirin/Ac=anticoagulant/GPA=gastroprotective agent

Etoricoxib

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Gottesdiener 2002,[245,246] MSD Study 007, multicentre, USA 14 weeks (2 parts; only part 1 included)	Part 1 (6 weeks) Etoricoxib 5mg per day (5mg od) Etoricoxib 10mg per day (10mg od) Etoricoxib 30mg per day (30mg od) Etoricoxib 60mg per day (60mg od) Etoricoxib 90mg per day (90mg od) Placebo Part 2 (8 weeks) Etoricoxib 30mg per day (30mg od) Etoricoxib 60mg per day (60mg od) Etoricoxib 90mg per day (90mg od) Diclofenac 150mg per day (50 mg tds)	 117 114 102 112 112 60	 61.74 62.47 61.25 60.03 60.10 62.52	 76.9% 77.2% 65.7% 66.1% 67.9% 78.3%	 7.39 8.60 8.86 7.60 7.16 7.18	 100% 100% 100% 100% 100% 100% (used in last 25/30 days)	 NR (Allowed but not reported)	 0% 0% 0% 0% 0% 0% (Excluded)	

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Leung 2002 [247] International 12 week MSD Study 019	Etoricoxib 60mg per day (60mg od) Naproxen 1000mg per day (500 mg bd) Placebo	224 221 56	62.9 63.2 64.1	77 78 82	5.9 6.3 6.3	95 90 93	NR NR NR	NR NR NR	
Hunt 2003a [248] Multicentre, International. 12 weeks. MSD Study 029	Etoricoxib 120mg per day (120mg od) Ibuprofen 2400mg per day (800mg tds) Placebo	221 226 233	61 62 62	76 69 77	NR NR NR	46 39 42	8 8 11	2 7 4	
Zacher 2003 [249] International (outside USA) 6 weeks MSD Study 805	Etoricoxib 60mg per day (60mg od) Diclofenac 150mg per day (50mg tds)	256 260	63.1 63.0	81.3 79.6	7.5 7.5	Data is separately given for 11 NSAIDs: see table 1, pg 730	Not given	Aspirin > 100mg Excluded. (aspirin < 100mg ie cardioprotective dosage allowed)	

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Collantes 2002 [250] Multicentre, International 12 weeks MSD Study 025	Etoricoxib 90mg per day (90mg od) Naproxen 1000mg per day (500 mg bd) Placebo	353 181 357	53 52 52	81% 82% 82%	8 8 9	100% 100% 100%	NR NR NR	Aspirin <100 mg per day permitted – overall <3% took aspirin.	
Matsumoto 2002 [251] Multicentre, USA. 12 weeks MSD Study 024	Etoricoxib 90mg per day (90mg od) Naproxen 1000mg per day (500mg bd) Placebo	323 170 323	55 56 56	73% 77% 81%	9 10 9	100% 100% 100%	NR NR NR	Aspirin <100 mg per day permitted – overall <3% took aspirin	
Hunt 2003b [252] USA & Canada 12 weeks MSD Study 026	Etoricoxib 120mg per day (120mg od) Naproxen 1000mg per day (500 mg bd) Placebo	251 244 247	53 54 54	84% 83% 81%	NR NR NR	74% 77% 72%	10% 9% 9%	4% 5% 4%	

[a]Duration of follow-up [b]Dose per day [c]Number of randomised [d]Values are means unless otherwise specified
[c]S=steroid/A=aspirin/Ac=anticoagulant/GPA=gastroprotective agent

Meloxicam

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Carrabba et al (1995) [166,167] Italy & Germany (24 centres) 3 weeks	Meloxicam 15mg per day (15mg od) Piroxicam 20mg per day (20mg od)	216 109+	61 62	85 84	5.8 5.9	Not stated	-	-	
Hosie et al (1996) [168] UK 6-months	Meloxicam 7.5mg per day (7.5 mg od) Diclofenac SR 100mg per day (100mg od)	169 167*	64 64	59 59	5.6 7.0	Not reported	-	-	
Linden et al (1998) [169] 22 centres (Sweden, Denmark, Belgium & Netherlands) 6 weeks	Meloxicam 15mg per day (15mg od) Meloxiam 30mg per day (30mg od) Peroxicam 20mg per day (20mg od)	129 ?? 127	67 ?? 67	63 ?? 63	6.2 ?? 5.5	Not stated	-	-	
Goei The et al (1997) [170] Belgium, Germany & Netherlands (23 centres) 6 weeks	Meloxicam 15mg per day (15mg od) Meloxicam 30mg per day (30mg od) Diclofenac SR 100mg per day (100mg od)	128 ?? 130	72 ?? 71	15 ?? 18	7.6 ?? 7.3	Not stated	-	-	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Hosie et al (1997) [171] UK 6-months	Meloxicam 15mg per day (15mg od) Perioxicam 20mg per day (20mg od)	306 149	66+ 64+	58 54	5 5	Not stated	-	-	
Dequeker J SELECT Trial (1998). [172] International. 28 days.	Meloxicam 7.5mg per day (7.5mg od) Piroxicam 20mg per day (20mg od)	4320 4336	61.3 61.6	68% 67%	3.8 4.0	79 79	6.4 5.6	Proportions not available.	
Hawkey C et al MELISSA Trial (1998). [173] International. 28 days.	Meloxicam 7.5mg per day (7.5mg od) Diclofenac SR 100mg per day (100mg od)	4635 4688	61.5 61.7	66.8% 67.2%	4.3 4.0	81.9 82.1	4.8 5.3	Proportions not available.	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Lund et al (1998) [174,175] Multicentre (Sweden, Denmark, Belgium, Netherlands & Germany) 3 weeks	Meloxicam 7.5mg per day (7.5mg od) Meloxicam 15mg per day (15mg od) Meloxicam 30mg per day (30 mg od) Placebo	140 134 - 137	70 68 - 68	64 75 - 75	8.7 8.5 - 8.0	Not reported	-	-	
Yocum et al (2000) [176,177 178] USA 12 weeks	Meloxicam 3.75mg per day (3.75mg od) Meloxicam 7.5mg per day (7.5mg od) Meloxicam 15mg per day (15mg od) Diclofenac 100mg per day (50 mg bd) Placebo	154 154 156 153 157	62 62 64 63 62	67 63 64 68 65	9 8 7 9 8	100 100 100 100 100	-	-	
Chang et al (2001) [179] Taiwan 4 weeks	Meloxicam 7.5mg per day (7.5mg od) Piroxicam 20mg per day (20mg od)	36 36	61 63	89 75	2.8 5.9	100 100	-	-	
Valat (2001) [180] Belgium, Italy & France (10 centres) 2-weeks	Meloxicam 7.5mg per day (7.5mg od) Diclofenac SR 100mg per day (100mg od)	117 112	58 57	86 88	9.2 10.1	NR NR	NR NR	NR NR	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Xu (2002) [181] China Multicentre, 4 weeks	Meloxicam 7.5mg per day (7.5mg od) Nabumetone 1000mg per day (1000mg od)	31 29	54 55	90 83	NR NR	NR NR	NR NR	NR NR	
Wojtuleswski et al (1996) [182,183] 48 centres (Europe & Mexico) 6-months	Meloxicam 7.5mg per day (7.5mg od) Naproxen 750mg per day (250mg tds)	199 180	18-75 18-75	No stated	9.3 9.2	172 (86) 168 (93)	-	-	
Lemmel et al (1997) [184,185] 59 centres Europe & Mexico 3- weeks	Meloxicam 7.5mg per day (7.5mg od) Meloxicam 15mg per day (15mg od) Placebo	159 162 147	55 54 55	Not stated	10.1 10.0 10.2	Not stated	-	-	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Furst et al (2002) [186,187] USA 12 weeks	Meloxicam 7.5mg per day (7.5mg od) Meloxicam 15mg per day (15mg od) Meloxicam 22.5mg per day (22.5mg od) Diclofenac 150mg per day (75 mg bd) Placebo	175 184 177 181 177	56 56 57 55 56	79 76 73 78 75	10 10 10 10 10	100 100 100 100 100	-	-	
Xu (2002b), [188,189] China, 4 weeks	Meloxicam 15mg per day (15mg od) Nabumetone 1000mg per day (1000mg od)	59 61	46 47	79.7 86.9	5.8 5.2	NR NR	NR NR	NR NR	

[a]Duration of follow-up [b]Dose per day [c]Number of randomised [d]Values are means unless otherwise specified
[e]S=steroid/A=aspirin/Ac=anticoagulant/GPA=gastroprotective agent

Rofecoxib

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Ehrich 1999 [191] Multicentre, USA. 6 week MSD Study 010	Rofecoxib 125mg per day (125mg od) Rofecoxib 25mg per day (25 mg od) Placebo	74 73 72	63.9 64.0 62.6	59.5% 80.8% 73.6%	11.3 12.0 12.2	100% 100% 100%	0 0 0	Unclear but appear to be excluded.	
Laine 1999 [192] Multicentre, USA. 12 week for primary outcome MSD Study 044/045	Rofecoxib 50mg per day (50mg od) Rofecoxib 25mg per day (25mg od) Ibuprofen 2400mg per day (800 mg tds) Placebo	186 195 183 177	62 62 62 61	69% 69% 66% 66%	NR NR NR NR	Overall 93%	18% 22% 19% 18%	Low dose aspirin not permitted.	
Cannon 2000 [193,194] Multicentre, USA. 12 months MSD Study 035	Rofecoxib 12.5mg per day (12.5mg od) Rofecoxib 25mg per day (25mg od) Diclofenac 150mg per day (50mg tds)	259 257 268	62.8 62.8 62.5	65.3% 68.1% 69.0%	11.1 11.5 11.4	92.7% 92.6% 90.3%	NR NR NR (allowed but not reported)	Patients on aspirin were excluded	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Day 2000 [195,196] Multicentre, International. 6 weeks. MSD Study 040	Rofecoxib 12.5mg per day (12.5mg od) Rofecoxib 25mg per day (25mg od) Ibuprofen 2400mg per day (800mg tds) Placebo	244 242 249 74	64.9 62.8 64.1 63.1	81 79 78 85	8.3 8.5 9.0 9.3	91 87 92 91	NR NR NR NR	Patients requiring aspirin at any dose were excluded.	
Hawkey (2000) [213] International (36 centres) 12 weeks 24 weeks MSD Study 044/045	Rofecoxib 25mg per day (25mg od) Rofecoxib 50mg per day (50mg od) Ibuprofen 2400mg per day (800mg tds) Placebo	195 193 193 194	62 61 61 62	77% 72% 74% 75%	NR NR NR NR	Overall 49.4% patients had prior NSAIDs within 30 days of the start of the study	12% 10% 13% 9%	Aspirin not allowed.	

Author/trial name (year) Country Duration[a]	**Intervention & comparator[b]**	**N[c]**	**Age (years)[d]**	**% female**	**Disease duration (years)[d]**	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Saag K, et al (2000a)[197] Multicentre, USA 6 week MSD Study 033	Placebo Rofecoxib 12.5mg per day (12.5mg od) Rofecoxib 25mg per day (25mg od) Ibuprofen 2400mg per day (2400mg od)	69 219 227 221	62 60 62 61	81.2% 76.3% 71.4% 73.8%	9 10 11 10	87 90.4 91.2 90.1	NR NR NR NR	Excluded from entry.	
Saag K, et al (2000b)[197] Multicentre, International. 1 year MSD Study 034	Rofecoxib 12.5mg per day (12.5mg od) Rofecoxib 25mg per day (25mg od) Diclofenac 150mg per day (150mg od)	231 232 230	62 62 63	81.0 77.7 81.7	8 9 9	88.7 89.7 89.1	NR NR NR	Excluded from entry.	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Acevedo 2001 [198] International (6 countries) 6 weeks MSD Study 902	Rofecoxib 12.5mg per day (12.5mg od) Arthrotec (diclofenac 100mg + misoprostol 400ug per day) (diclofenac 50mg + misoprostol 200ug bd)	242 241	61.8 62.4	79.3% 81.3	6.8 8.5	66.5 58.9	-	-	
Ehrich 2001 [199,200] [201,202] [203] Multicentre, USA. 6 week MSD Study 029	Placebo Rofecoxib 5 mg Rofecoxib 12.5 mg Rofecoxib 25 mg Rofecoxib 50 mg	145 149 144 137 97	61.4 61.2 61.4 63.0 61.3	68.3% 71.8% 71.5% 75.9% 66.0%	10.3 11.6 11.4 9.4 12.0	100% 100% 100% 100% 100%	-	-	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Truitt 2001 [204] Multicentre, USA. 6 week MSD Study 058	Placebo Rofecoxib 12.5 mg Rofecoxib 25 mg Nabumetone 1500 mg	52 118 56 115	83.0 83.3 83.8 83.1	65.4% 65.3% 57.1% 64.3%	12.3 17 14 14.6	76.9% 75.4% 76.8% 74.8%	13.5 9.3 17.9 6.1	36.5 32.2 41.1 27.8	
Geba 2002 [263] (VACT-1) USA 6 weeks	Paracetamol 4000mg per day (1000mg qds) Celecoxib 200mg per day (200mg od) Rofecoxib 12.5mg per day (12.5mg od) Rofecoxib 25mg per day (25mg od)	94 97 96 95	63.1 62.6 63.4 61.3	70.2 64.9 65.6 72.6	>0.5 >0.5 >0.5 >0.5	76.6 79.4 75 76.8	NR NR NR NR	NR NR NR NR	
Myllykangas-Luosujärvi 2002, [205] Multinational (2 identical RCTs combined) 6 weeks MSD Study 901	Rofecoxib 12.5 mg per day (12.5mg od) Naproxen 1000mg per day (500 mg bd)	471 473	61.9 61.3	80.3% 76.5%	Not reported	89.2% 89.9% (chronic use)	3.6% 4.4%	Proportion not reported. Aspirin >100mg/day excluded.	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Niccoli (2002) [190] Italy 2 weeks	Rofecoxib 25mg per day (25mg od) Diclofenac 150mg per day (150mg od) AMG 3600mg per day (1200 mg tds) plus 600mg per day (600mg od)	30 30 30	72.42 71.06 73.27	60.0 63.3 60.0	CT	CT	-	-	
Lisse (2003) [206] ADVANTAGE study. USA & Sweden. 12 weeks MSD Study 102/903	Rofecoxib 25mg per day (25mg od) Naproxen 1000mg per day (1000mg od)	2785 2772	63 63	71 71	Overall 92% had symptoms > 1 year	92% 92%	47% 47%	Overall 13% of patients on low dose aspirin (≤100 mg). Patients on higher doses of aspirin not included.	
Kivitz (2004) [207] US 6 weeks MSD Study 085	Rofecoxib 12.5mg per day (12. 5mg od) Nabumetone 1000mg per day (1000mg od) Placebo	424 410 208	63.6 62.2 64.1	68% 70% 67%	6.4 5.9 6.1	96.5 93.7 95.7	18.6 18.5 15.9	10.8 13.9 10.1	

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Schnitzer J(1999)[208] Multicentre, US 8 weeks MSD Study 068	Placebo Rofecoxib 5 mg Rofecoxib 25 mg Rofecoxib 50 mg	168 158 171 161	54.7 54.8 55.7 54.4	72% 75.9% 78.9% 80.7%	8 11 9 10	100% 100% 100% 100%	NR NR NR NR	NR NR NR NR	
Bombardier (2000)[209,210,211] International. Median 9 months. VIGOR Study	Rofecoxib 50mg per day (50mg od) Naproxen 1000mg per day (1000mg od)	4047 4029	58 58	79.6 79.8	10.9 10.7	82.1% 82.7%	7.7% 7.8%	0 0	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Geusens PP et al (2002)[212] International multi-centre 12 weeks MSD Study 097	Placebo Rofecoxib 25 mg Rofecoxib 50 mg Naproxen 1 g	289 306 286 142	53.7 52.9 53.7 54.1	84.8% 80.1% 83.9% 82.4%	8.6 8.2 8.6 9.1	100% 100% 100% 100%	NR NR NR NR	0 0 0 0	
Hawkey (2003) International (18 countries) 12 weeks MSD Study 098/103	Rofecoxib 50mg per day (50mg od) Naproxen 1000mg per day (500mg bd) Placebo	219 220 221	53 51 51	86% 78% 82%	NR NR NR	68% 57% 70%	-	-	

[a]Duration of follow-up [b]Dose per day [c]Number of randomised [d]Values are means unless otherwise specified
*S=steroid/A=aspirin/Ac=anticoagulant/GPA=gastroprotective agent

Valdecoxib

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Fiechtner 2001 Pfizer Study 015 USA, 6 weeks	Valdecoxib 1mg per day (0.5 mg bd) Valdecoxib 2.5mg per day (1.25 mg bd) Valdecoxib 5mg per day (2.5 mg bd) Valdecoxib 10mg per day (5 mg bd) Valdecoxib 10mg per day (10 mg od) Valdecoxib 20mg per day (10 mg bd) Naproxen 1000mg per day (500 mg bd) Placebo	77 81 83 83 82 79 75 82	62.6 63.5 63.1 61.5 63.2 61.8 60.6 62.4	69% 72% 67% 70% 78% 68% 72% 55%	9.7 9.8 10.1 8.3 8.6 9.4 8.1 9.2	NR	10% 10% 13% 11% 13% 11% 11% 17%	Allowed but proportion not reported	
Kivitz 2002 [254] US and Canada (85 centres) 12 weeks Pfizer Study 053	Valdecoxib 5mg per day (5mg od) Valdecoxib 10mg per day (10mg od) Valdecoxib 20mg per day (20mg od) Naproxen 1000mg per day (500 mg bd) Placebo	201 206 202 205 205	58.7 59.8 59.6 60.4 60.3	64% 65% 67% 63% 64%	9.8 8.7 9.2 9.4 8.3	NR NR NR NR NR	10% 12% 14% 15% 10%	May be allowed but not clearly reported	

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Makarowski 2002, [255] USA & Canada 12-weeks Pfizer Study 049	Valdecoxib 5mg per day (5mg od) Valdecoxib 10mg per day (10mg od) Naproxen 1000mg per day (500 mg bd) Placebo	120 111 118 118	60.4 63.9 63.1 62.1	67% 66% 69% 69%	6.4 6.5 5.3 6.2	NR NR NR NR	8% 13% 9% 11%	Allowed but % not reported	
Sikes 2002 [256] USA/Canada 12 weeks Pfizer Study 048	Valdecoxib 10mg per day (10mg od) Valdecoxib 20mg per day (20mg od) Ibuprofen 2400mg per day (800 mg tds) Diclofenac SR 150mg per day (75 mg bd) Placebo	204 219 207 212 210	58.6 60.1 60.2 61.1 59.5	66% 70% 67% 69% 69%	9.8 11.9 9.9 10.8 9.4	Not reported (but requiring chronic use of NSAIDs and/or oral analgesics was an inclusion criteria)	13% 14% 14% 15% 11%	9-18% across treatment groups.	

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Moskowitz 2003,[264] USA and Canada, multicentre, 2 weeks Pfizer Study 143	Valdecoxib 10mg per day (10mg od) Rofecoxib 25mg per day (25mg od) Placebo	212 208 110	63.3 64.6 63.9	63% 66% 66%	7.5 to 8.1	25.0% to 44.7% (NSAIDs, COX-2 inhibitors, analgesics)	4% to 8%	-	
Pfizer Study 063 country?? 26 weeks	Valdecoxib 10mg per day (10 mg od) Valdecoxib 20mg per day (20mg od) Diclofenac SR 150mg per day (75 mg bd)	259 261 262	63 (overall)	?	9 (overall)	100%? (requiring NSADIs to control symptom)	13% (overall)	13% (overall)	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Pfizer Study 047 USA and Canada, 26 wks OA and RA, 14 wks RA	Valdecoxib 40mg per day (20mg bd)	399	56.2	71.9 (287)	OA:9.8(N =242) RA:10.2(N=199)	100	Hx GI bleed 6/ 399 (1.5%) Hx GI ulcer 42/ 399 (10.5%)	54/ 399 (13.5%)	
	Valdecoxib 80mg per day (40mg bd)	404	56.1	71.8 (290)	OA:9.7(N =242) RA:9.9(N =210)	100	Hx of GI bleed 7/ 404 (1.7%) Hx GI ulcer 42/ 404 (10.4%)	46/ 404 (11.4%)	
	Naproxen 1000mg per day (500mg bd)	415	55.8	71.1 (295)	OA:9.1(N =235) RA:11.6(N=215)	100	Hx of GI bleed 7/ 415 (1.7%) Hx GI ulcer 46/ 415 (11.1%)	58/ 415 (14.0%)	
						Discontinue at or before screening	No GI ulceration within 30d of 1st dose, no active GI disease	Allowed if for CV prophylaxis ≥ 30d before 1st dose, could continue on regimen	
Bensen 2002 [257] Canada & USA 12 weeks Pfizer Study 60	Valdecoxib 10mg per day (10 mg od)	209	55.3	75%	10.0	100%	8.1%	Permitted but proportions not reported.	
		212	55.3	71%	10.0	100%	9.4%		
	Valdecoxib 20mg per day (20 mg od)	221	54.9	79%	9.4	100%	8.1%		
	Valdecoxib 40mg per day (40 mg od)	226	55.4	81%	9.9	100%	8.0%		
	Naproxen 1000mg per day (500 mg bd)	222	55.7	77%	10.3	100%	8.1%		
	Placebo								

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Pavelka 2003,[258] International, 26 weeks Pfizer Study 062	Valdecoxib 20mg per day (20 mg od) Valdecoxib 40mg per day (40 mg od) Diclofenac SR 150mg per day (75 mg bd)	246 237 239	55.7 54.8 56.4	73% 71% 80%	9.9 10.6 10.0	Not reported	10.6% 5.9% 5.9%	5.7% 5.9% 5.4%	
Pfizer 016 USA, 6 weeks	Valdecoxib 1mg per day (0.5 mg bd) Valdecoxib 2.5mg per day (1.25 mg bd) Valdecoxib 5mg per day (2.5 mg bd) Valdecoxib 10 mg per day (5 mg bd) Valdecoxib 10mg per day (10 mg od) Valdecoxib 20mg per day (10 mg bd) Naproxen 1000mg per day (500 mg bd) Placebo	89 84 83 85 81 82 87 87	56.9 (SD 12.04), range 20-85	N=522 (77%)	Between 9.3 and 11.7 years depending on treatment group (overall 10.65)	Not stated	2.3-7.1% history of GI bleeding; 9.2-19.0% history of gastroduodenal ulcer	Allowed, but number of patients not stated	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Pfizer Study 061, USA, 12 weeks	Valdecoxib 10 mg per day (10mg od) Valdecoxib 20mg per day (20mg od) Valdecoxib 40mg per day (40mg od) Naproxen 1000mg per day (500mg bd) Placebo	226 219 209 219 220	56.8 55.1 56.9 54.5 58.1	78% 83% 74% 75% 73%	12.0 11.1 10.5 10.4 11.5	99% (n=1086)	History of upper GI bleeding 1.6% (n=18); history of gastroduodenal ulcer 11% (n=115)	≤325mg/d aspirin allowed for non-arthritic reasons if been taking for at least 30 days; number of patients not stated	

[a]Duration of follow-up [b]Dose per day [c]Number of randomised [d]Values are means unless otherwise specified
[e]S=steroid/A=aspirin/Ac=anticoagulant/GPA=gastroprotective agent

Head to head OA

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
McKenna 2001b[145] USA 20 centres 6-weeks, Pfizer Study 152	Celecoxib 200mg per day (200mg od) Rofecoxib 25mg per day (25mg od) Placebo	63 59 60	62 61.5 63	67 71 75	11.2 10.1 11.5	71 81 83	51 56 67	NR NR NR	

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Whelton 2001 [260,450] SUCCESS VI US and Canada (101 centres) 6 weeks, Pfizer Study 149	Celecoxib 200mg per day (200mg od)	411	74.0	66.5%	13.6	NR	NR	NR	
	Rofecoxib 25mg per day (25mg od)	399	74.1	66.4%	11.7	NR	NR	NR	
Whelton 2002a,[261] SUCCESS VII, US & Canada. 6 weeks, Pfizer Study 181	Celecoxib 200mg per day (200mg od)	549	73.3	63.9	11.7	NR	NR	NR	
	Rofecoxib 25mg per day (25mg od)	543	73.1	60.1	10.1	NR	NR	NR	

Author/trial name (year) Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)*	Concurrent low dose (≤325mg/d) aspirin (%)*	
Gibofsky 2003 [150] US and Canada 6 weeks, Pfizer Study 003	Celecoxib 200mg per day (200mg od) Rofecoxib 25mg per day (25mg od) Placebo	189 190 96	62.2 63.4 63.1	69% 66% 65%	8.6 8.8 8.3	Reported "similar across all three groups"	NR NR	NR NR	
Sowers 2003 [262] Pfizer 002, CRESECENT 65 Centres North America, Europe & Chile 12 weeks	Celecoxib 200mg per day (200mg od) Rofecoxib 25mg per day (25 mg od) Naproxen 1000mg per day (500mg bd)	136 138 130	61 62 64	62 59 60	NR NR NR	NR NR NR	NR NR NR	NR NR NR	
Geba 2002 [263] VACT-1 USA 6 weeks	Paracetamol 4g per day (1g qds) Celecoxib 200mg per day (200mg od) Rofecoxib 12.5mg per day (12.5mg od) Rofecoxib 25 mg per day (25mg od)	94 97 96 95	63.1 62.6 63.4 61.3	70.2 64.9 65.6 72.6	>0.5 >0.5 >0.5 >0.5	76.6 79.4 75 76.8	NR NR NR NR	NR NR NR NR	

Author/trial name (year) Country Duration[a]	**Intervention & comparator**[b]	**N**[c]	**Age (years)**[d]	**% female**	**Disease duration (years)**[d]	**Prior NSAIDs (%)**	**Prior GI events (%)***	**Concurrent low dose (≤325mg/d) aspirin (%)***	
Moskowitz 2003 [264] Pfizer Study 143 USA and Canada, multicentre, 2 weeks	Valdecoxib 10mg per day (10mg od) Rofecoxib 25mg per day (25mg od) Placebo	212 208 110	63.3 64.6 63.9	63% 66% 66%	7.5 to 8.1 (data for individual arms not provided)	25.0% to 44.7% (NSAIDs, COX-2 inhibitors, analgesics)	4% to 8% (data for individual arms not provided)	Allowed but proportion not reported	

[a]Duration of follow-up [b]Dose per day [c]Number of randomised [d]Values are means unless otherwise specified
[c]S=steroid/A=aspirin/Ac=anticoagulant/GPA=gastroprotective agent

Appendix 6: Details of quality assessment of included randomised controlled trials

Celecoxib

Author (year)	Appropriate method of randomisation	Adequate concealment	Double blind	Intention to treat analysis	Loss to follow up (% each arm)	Total Jadad score /5
Simon (1998a)[138]	Y	CT	Y	Y*	NR	3
Bensen (1999) [139-141]	CT	Y	Y	Y	1% (not listed per group)	5
Williams (2000) [142]	Y	CT	Y	Y*	<1% 2% <1%	5
Goldstein (2001b)[143] (Pfizer 2004 submission)	Yes	Yes	Yes	Yes	All <1%	5
Kivitz (2001) [144]	Can't tell	Y [block randomisation]	Y	Y	1.9% 0% 0.9% 0.5% 0.9%	3
McKenna et al (2001b) [145]	Y	CT	Y	Y*	1.6 0 3.3	5
McKenna (2001a) [146]	CT	CT	Yes	Yes	0.3%+	3
Pfizer Study 021 (2000 submission)	Y	CT	Y	Y	Y	5
McKenna (2002) [147]	Y	CT	Y	CT	CT	3
Pfizer Study 047 (1997) (2000 submission)	Y	CT	Y	Y	0/1/1/0	5
Whelton (2002) [260,450]	Y	Y	Y	Y	Y Cele=1/411 Rofe=2/399	5
Williams (2001) [148]	CT	CT	Y	Y*	1% 0% 1%	5
Suarez-Otero (2002) [149]	N	N	Y	CT	CT	3
Whelton et al (2002a)[261]	Y	Y	Y	Y	<1% both arms	5
Gibofsky (2003)[150]	Y	Y	Y	Y	Y Cele=1/189 Rofe=0 Plac=1/96	5
Hawel (2003) [151]	CT	CT	Y	Y	CT	4

Author (year)	Appropriate method of randomisation	Adequate concealment	Double blind	Intention to treat analysis	Loss to follow up (% each arm)	Total Jadad score /5
Pincus PACESa (2004)[152,153]	CT	CT	N	Y	CT	1
Pfizer Study 002 (2002) (2004 submission)	Y	Y	Y	Y	0% <1% 1.5%	5
Pincus PACESb (2004)[152]	CT	CT	N	Y	CT	1
Simon (1998b)[138]	Y	CT	Y	Y*	NR	3
Emery (1999)[154]	Y	CT	Y	Y	0.6% 0.3%	5
Simon (1999)[155,156]	Yes	Yes	Yes	Yes	0.4% 1.3% 0.5% 0.4% 1.3%	5
Pfizer Study 023 (1998) (2000 submission)	Y	Y	Y	Y	0% 0% 0% <1% 0%	5
Silverstein CLASS study (2000)[157-161 162,163]	Y	Y	Y	Y	0%	5
Goldstein (2001)[164]	CT	CT	Y	Y*	<1%/2%	5
Pfizer Study 071 (1998) (2000 submission)	Y	Y	Y	Y	1% <1% 1%	5
Chan (2002)[165]	Y	Y	Y	Y	0.7% 0.7%	5
Pfizer Study 105 (2000) (2004 submission)	Y	Y	Y	Y	4.8%/5.3%	5
Pfizer Study 106 (2000) (2004 submission)	Y	Y	Y	Y	4.8%/3.2%	5
Pfizer Study 107 (2000) (2004 submission)	Y	Y	Y	Y	0%/0%	5

Y=Yes N=NO CT=can't tell

Etodolac

Author (year)	Appropriate method of randomisation	Adequate concealment	Double blind	Intention to treat analysis	Loss to follow up (% each arm)	Total Jadad score /5
Bacon (1990a) [217,218]	CT	CT	Y	N	CT	?2 - not enough detail in overview or interim papers
Bacon (1990b) [217,218]	CT	CT	Y	N	CT	?2 - not enough detail in overview or interim papers
Bacon (1990c) [217,218]	CT	CT	Y	N	CT	?2 - not enough detail in overview or interim papers
Williams (1989)[219]	CT	CT	Y	N	Y	3
Freitas (1990) [220]	CT	CT	Y	N	CT	4
Brasseur (1991)[221]	CT	CT	1	N	Y	4
Karbowski (1991)[222]	CT	CT	Y	N	Y Eto=0 Ind=1/33	3
Palferman (1991)[223]	CT	CT	Y?	N	Y Etodolac 5/29 Naproxen 5/27	4
Paulsen (1991)[224]	CT	CT	CT	N	Y Eto=2/112 Piro=3/108	3
Pena (1991)[225]	CT	CT	CT	N	Y Etodolac 1/31 Naproxen 0/31	3
Perpignano (1991)[226]	Y ?	CT	Y	N (drop-outs not included in efficacy analysis, as treatment period too brief; no clinical change at time of side effects occurring) Y (tolerability)	0/10 (0%) ET arm; 2/10 (20%) NAP arm	
Dick (1992) [227]	Y	CT	Y	CT	ET 1.7% PIR 1.7%	3
Grisanti 1992 [228]	CT	CT	Y	N	CT	3
Waterworth (1992)[229]	ct	ct	y	ct	Y Eto=26/28 Piro=28/29	3

Author (year)	Appropriate method of randomisation	Adequate concealment	Double blind	Intention to treat analysis	Loss to follow up (% each arm)	Total Jadad score /5
Burssens (1993)[230]	CT	CT	Y	Y	0%	2
Eisenkolb (1993)[231]	Y	CT	Y	CT	ET 1.5% DIC 0%	3
Chikanza (1994)[232]	CT	Y (outside pharmacy prepared drugs)	Y	Y	Y E-N=32/39 N-E=24/37	4
Lucker (1994)[233]	Y	Y	Y	N	CT See table 3, but actual Loss to FU not given	5
Perpignano (1994)[234]	Y	Y (distance randomisation)	Y	Y (partly)	Y Eto = 2/60 Teno= 1/60	5
Dore (1995) [235]	CT	Y	Y	Y (although not explicitly stated, no. randomised and no. analysed tally up.)	CT (although withdrawals and reasons stated – no comment on loss to FU)	4
Schnitzer (1995)[236]	CT	CT	Y	Y	Y Eto=0 Nab=0 Plac=1/90	4
Jennings (1997)[237]	CT	CT	CT	N	N	2
Rogind (1997)[238]	CT	CT	Y	N	Y Eto=3/138 Piro=3/133	4
Schnitzer (1997)[239]	CT	CT	Y	Y*	0%	4
Taha (1989) [240,241]	CT	CT	Y	N	CT	2
Delcambre (1990)[207]	CT	CT	Y	Partly*	Not clear which arms original 3 drop-outs were in; subsequent drop-outs due to adverse events and inefficiency: 10/49 (20.4%) from ET arm and 12/50 (24.0%) from IND arm	4
Taha (1990) [241,242]	CT	CT	Y	N	CT?	2
Lightfoot (1997)[243]	Y	CT	Y	N	CT	4? *Assessed as 3 by JD*
Neustadt (1997)[244]	Y	CT	Y	CT	CT	3

Y=Yes N=NO CT=can't tell

Etoricoxib

Author (year)	Appropriate method of randomisation	Adequate concealment	Double blind	Intention to treat analysis	Loss to follow up (% each arm)	Total Jadad score /5
Gottesdiener et al (2002) [245,246] (PART 1)	Y	Y	Y	Y?	E5 10.3% E10 14.9% E30 7.8% E60 8.0% E90 9.8% PL 16.7%	5
Leung et al (2002) [247]	Y	Y	Y	CT	<5% overall	5
Hunt (2003a) [248]	CT	CT	CT	CT	Y	3
Zacher 2003 [249]	Y	Y	Y	Y	92% completed the study; no breakdown by trial arm	4
Collantes (2002) [250]	CT	CT	Y	CT	This has been grouped under "discontinued for other reasons" one of which is Loss to fu: therefore individual % are not available.	3
Matsumoto (2002) [251]	CT	CT	Y	Y	CT	3
Hunt (2003b) [252]	Y	Y	Y	Y	ETO 0.4 NAP 0.0 PL 0.4	5

Y=Yes N=NO CT=can't tell

Meloxicam

Author (year)	Appropriate method of randomisation	Adequate concealment	Double blind	Intention to treat analysis	Loss to follow up (% each arm)	Total Jadad score /5
Carrabba et al (1995) [167]	CT	CT	N*	Y	0% 1%	1
Hosie et al (1997) [168]	CT	CT	Y	Y	Not reported	3
Linden et al (1996) [169]	CT	CT	CT	Y*	CT	3
Goei The et al (1997)	CT	CT	Y	Y	CT	2
Hosie et al (1997) [171]	CT	CT	Y	Y	CT+	3
Dequeker SELECT (1998) [172]	CT	CT	Y	Y	unclear	3+ not sufficient detail in paper
Hawkey C (1998) [173]	CT	CT	Y	Y	10% meloxicam 12% diclofenac	3+ not enough info in paper
Lund et al (1998) [174] [175]	CT	CT	Y	Y*	0 0 Not reported -	3
Yocum et al (2000) [176-178]	CT	CT	Y	Y	0.6+	3
Chang et al (2001) [179]	CT	CT	Yes	Yes	1/36 2/36	4
Valat (2001) [180]	CT	CT	Y	Y	5.9% 11.7%	4
Xu (2002a) [181]	Y	CT	Y	N	Y (1/32 meloxicam; 1/31 nabumetone)	5
Wojtulewski et al (1996)	CT	CT	Y	Y	Not stated	4
Lemmel et al (1997)	CT	CT	Y	Y	Not stated	3
Furst et al (2002) [186,187]	Y	CT	Y	Y+	Not stated ++	4
Xu (2002b) [188,189]	Y	CT	Y	N	CT*	4

Y=Yes N=NO CT=can't tell

Rofecoxib

Author (year)	Appropriate method of randomisation	Adequate concealment	Double blind	Intention to treat analysis	Loss to follow up (% each arm)	Total Jadad score /5
Ehrich (1999) [191]	Y	Y	Y	Y	<2% all groups	5
Laine (1999) [192]	Y	Y	Y	Y	<12% all groups	5
Cannon (2000) [193,194]	Y	Y CT? (yenfu)	Y	CT	<2% all groups	5
Day (2000) [195,196]	Y	Y	Y	Y	<3% ?	5 o 4 ? see below
Hawkey (2000) [213]	CT	CT	Y	Y	Y But numbers not reported	4
Saag (2000a) [197]	Y	Y	Y	Y	<3% all groups	5
Saag (2000b) [197]	Y	Y	Y	Y	<15% all groups	5
Acevedo (2001) [198]	Y	CT	Y	Y	Y But rates not reported.	5
Ehrich (2001) [199-201] [2022559}	TABLE IN DRUG FOLDER BUT BLANK					
Truitt (2001a) [204]	Y	Y	Y	Y	<7.5% all groups	5
Geba (2002) [263]	Y	Y	Y	Y	<2.5% all groups	5
Myllykangas (2002) [205]	Y	Y	Y	Y	Y But the numbers are not given.	5
Niccoli (2002) [190]	Y	CT	N	N	0	1
Lisse (2003) [206]	Y	Y	Y	Y	<2.5% both arms	5
Kivitz (2004) [207]	Y	Y	Y	Y	1.2% rofecoxib 0.2% nabumetone, 0% placebo	5
Schnitzer (1999) [208]	Y	Y probably – but insufficient detail	Y	Y	<5% each arm	4/5
Bombardier VIGOR Study (2000) [209,210] [211]	Y	Y	Y	Y	<7% both arms	5
Geusens (2002) [212]	Y	CT	Y	Y	CT	3
Hawkey (2003) [215]	CT	CT	Y	Y	Y Plac=1/221 Rofe=0/219 Nap=1/220	4

Y=Yes N=NO CT=can't tell

Valdecoxib

Author (year)	Appropriate method of randomisation	Adequate concealment	Double blind	Intention to treat analysis	Loss to follow up (% each arm)	Total Jadad score /5
Fiechtner (2001)[451]	Y	CT	Y	Y	Y	5
Kivitz (2002) [254]	Y	Y	Y	Y	Y Placebo=0 Val 5mg=0 Val 10mg=1/206 Val 20mg=1/202 Nap=1/205	5
Makarowski (2002) [255]	CT	CT	Y	Y	<2% all groups	3+
Sikes (2002) [256]	Y	CT	Y	Y?	V10 0% V20 2.3% IBU 0.5% DIC 0.5% PL 1%	4
Moskowitz (2003)[264]	Y	Y	Y	Y	Y	5
Pfizer Study 063	Y	?	Y		Y	5
Pfizer Study 047 N91-99-02-047	Y	Y	Y	Y	Y	5
Bensen (2002) [257]	CT	CT	Y	Y	<1% all groups	3+ details not reported
Pavelka (2003) [258]	Y	Y CT?	Y	Y	<0.5% all groups.	5
Pfizer Study 016	Y	CT	Y	Y?*	223/678 (32.9%)	5
Pfizer Study 061	+1	CT	+1	?*	7/1093 (1%)	5/5

Y=Yes N=NO CT=can't tell

Appendix 7: Details of included economic evaluations

Study: Zabinski RA et al. An economic model for determining costs and consequences of using various treatment alternatives for the management of Arthritis in Canada. *Pharmacoeconomics 2001;19(suppl 1):49-58*

Study design	
The research question, including description of alternatives being compared	For patients with OA or RA, comparison of celecoxib and various NSAID/GI protective regimes, in Canada.
The viewpoint(s) of the analysis	Ministry of Health
The form of economic evaluation used	Cost-consequence
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	Pooled analysis of 8 phase III trials
The primary outcome measure(s) for the economic evaluation	GI events, ulcers and deaths
Methods to value health states and other benefits, and subjects (if relevant)	N/A
Methods for the estimation of quantities and unit costs	Expert opinion for resource use. Standard health sector sources for unit costs
Currency and price data	Can $, 1998
Details of any model used	Decision tree model (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	6 months
The discount rate(s)	N/A
Details of statistical tests	None
Base case analysis results	Expected cost for celecoxib slightly higher than NSAID alone strategy but lower than all others. And celecoxib has the best profile for all outcome measures (e.g. serious GI events, deaths etc).
Details of sensitivity analysis	1 way sensitivity analyses – results most sensitive to probability of upper GI distress.
The answer to the study question?	"the use of celecoxib could result in the avoidance of a significant number of NSAID-attributable GI adverse events, and … would not impose an excessive incremental impact on the overall provincial healthcare budget."
Other issues	
Funding source	Pfizer & Pharmacia
MI effects included?	No

Study: Svarvar P & Aly A. Use of the ACCES model to predict the health economic impact of celecoxib in patients with osteoarthritis or rheumatoid arthritis in Norway. *Rheumatology* 2000;39(suppl 2):43-50

Study design	
The research question, including description of alternatives being compared	For patients either with RA or OA, comparison of celecoxib, NSAID monotherapy, and average NSAID use in Norway.
The viewpoint(s) of the analysis	Health sector
The form of economic evaluation used	CEA
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	[As in main publication on ACCES model]
The primary outcome measure(s) for the economic evaluation	GI events avoided Life years gained
Methods to value health states and other benefits, and subjects (if relevant)	N/A
Methods for the estimation of quantities and unit costs	Expert opinion
Currency and price data	Norwegian Krone, 1999
Details of any model used	Decision tree – ACCES model
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	N/A
Details of statistical tests	None
Base case analysis results	Celecoxib is dominant over all alternatives i.e. lower costs & more effective
Details of sensitivity analysis	Base case result holds for virtually all alternative scenarios considered
The answer to the study question?	"the introduction of celecoxib into the Norwegian NSAID market… will provide societal benefits at reduced costs".
Other issues	
Funding source	Pfizer
MI effects included?	No

Study: Haglund U & Svarvar P. The Swedish ACCES model: predicting the health economic impact of celecoxib in patients with osteoarthritis or rheumatoid arthritis. *Rheumatology* 2000;39(suppl 2):51-56

Study design	
The research question, including description of alternatives being compared	For patients either with RA or OA, comparison of celecoxib and NSAID monotherapy
The viewpoint(s) of the analysis	Health sector
The form of economic evaluation used	CEA
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	[As in main publication on ACCES model]
The primary outcome measure(s) for the economic evaluation	GI events avoided Life years gained
Methods to value health states and other benefits, and subjects (if relevant)	N/A
Methods for the estimation of quantities and unit costs	Expert opinion
Currency and price data	Swedish Krona, 1999
Details of any model used	Decision tree – ACCES model
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	N/A
Details of statistical tests	None
Base case analysis results	Celecoxib is dominant over all alternatives i.e. lower costs & more effective
Details of sensitivity analysis	Base case result holds for virtually all alternative scenarios considered
The answer to the study question?	"the use of celecoxib in the Sweden … will provide societal benefits … at reduced costs".
Other issues	
Funding source	Pfizer
MI effects included?	No

Study: Moore RA et al. Health economic comparisons of rofecoxib versus conventional nonsteroidal anti-inflammatory drugs for osteoarthritis in the United Kingdom. *Journal of Drug Assessment* 2001;4:21-37

Study design	
The research question, including description of alternatives being compared	For patients with OA, comparison of rofecoxib and conventional NSAID
The viewpoint(s) of the analysis	Health sectors only
The form of economic evaluation used	CEA
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	Rofecoxib phase IIb-III clinical trials. Uses data from 8 trials.
The primary outcome measure(s) for the economic evaluation	Life years saved PUB avoided
Methods to value health states and other benefits, and subjects (if relevant)	N/A
Methods for the estimation of quantities and unit costs	Expert opinion plus literature sources.
Currency and price data	UK £, 1996
Details of any model used	Decision tree (diagram shown)
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	N/A
Details of statistical tests	None
Base case analysis results	Cost/PUB avoided: £10,700. Cost/life year saved: £15,600.
Details of sensitivity analysis	Extensive 1 way SA undertaken. Results were most sensitive to the rate of prophylactic GPA use.
The answer to the study question?	"The importance of rofecoxib represents an important therapeutic advance… at only a modest additional cost."
Other issues	
Funding source	Merck
MI effects included?	No

Study: Fendrick AM et al. Role of initial NSAID choice and patient risk factors in the prevention of NSAID gastropathy: A decision analysis. *Arthritis & Rheumatism* 2002;47:36-43

Study design	
The research question, including description of alternatives being compared	Comparison of 2 strategies for long-term NSAID users: 1. generic NSAID used initially & safer NSAIDs reserved for patients experiencing GI adverse events or intolerance, and 2. safer NSAIDs first line for all patients.
The viewpoint(s) of the analysis	Third-party payer
The form of economic evaluation used	CEA
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	MUCOSA trial & Cox II trials
The primary outcome measure(s) for the economic evaluation	Complicated ulcer prevented
Methods to value health states and other benefits, and subjects (if relevant)	N/A
Methods for the estimation of quantities and unit costs	Mainly pricing & charging data
Currency and price data	US $. Price year not stated
Details of any model used	Markov model (diagram included)
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	N/A
Details of statistical tests	None
Base case analysis results	Strategy 2 (compared to strategy 1) was associated with ICERs of: • $31,900 per symptomatic ulcer avoided • $56,700 per complicated ulcer avoided
Details of sensitivity analysis	1-way SA undertaken. Results most sensitive to relative level of GI protection provided by the safer NSAIDs and the ulcer risk of the patient population.
The answer to the study question?	"Unrestricted use of NSAIDs… has the potential to produce important clinical benefits at incremental cost."
Other issues	
Funding source	Unrestricted educational grant from SKB
MI effects included?	No

Study: Tavakoli M. Modelling therapeutic strategies in the treatment of osteoarthritis. *Pharmacoeconomics* 2003;21(6):443-454

Study design	
The research question, including description of alternatives being compared	Comparison of 4 weeks treatment for OA with - meloxicam - diclofenac - piroxicam
The viewpoint(s) of the analysis	Health sector only
The form of economic evaluation used	Cost-minimisation analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	2 large RCTs, MELISSA and SELECT – pooled estimate used.
The primary outcome measure(s) for the economic evaluation	None
Methods to value health states and other benefits, and subjects (if relevant)	N/A
Methods for the estimation of quantities and unit costs	Published and routine data sources
Currency and price data	UK £, 1998 (except drug costs which at 2000 prices)
Details of any model used	Decision tree model (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	4 weeks
The discount rate(s)	N/A
Details of statistical tests	Monte Carlo simulation
Base case analysis results	Cost per patient Meloxicam £30 Piroxicam £35 MR Diclofenac £51
Details of sensitivity analysis	1 way and & probabilistic SA The SA results suggest "that this drug is the lowest cost option in the treatment of osteoarthritis".
The answer to the study question?	"Meloxicam is a cost saving drug"
Other issues	
Funding source	None - "The author did not receive any funding for conducting this study"
MI effects included?	Yes

Study: El-Serag HB et al. Prevention of complicated ulcer disease among chronic users of nonsteroidal anti-inflammatory drugs. *Arch Intern Med* 2002;162:2105-2110

Study design	
The research question, including description of alternatives being compared	For OA patients, 8 strategies compared: (1) ibuprofen, (2) ibuprofen + PPI, (3) ibuprofen + misoprostol, (4) celecoxib, and (5) → (8) comprised Helicobacter pylori treatment followed by each of the previous 4 strategies.
The viewpoint(s) of the analysis	Third-party payer
The form of economic evaluation used	CEA
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	Published estimates. Very little detail given on synthesis of data. Expert opinion in some cases.
The primary outcome measure(s) for the economic evaluation	Reduction in UGI events
Methods to value health states and other benefits, and subjects (if relevant)	N/A
Methods for the estimation of quantities and unit costs	Data on quantities not stated. Published sources for costs.
Currency and price data	US $, 1999
Details of any model used	Decision tree model (no diagram)
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	N/A
Details of statistical tests	None
Base case analysis results	Most cost-effective strategies were celecoxib and co-therapy with PPIs. But high ICERs (i.e. > $35000 per UGI event avoided) for celecoxib in patients with low risk of UGI events. Where risk is high, celecoxib is the dominant strategy
Details of sensitivity analysis	1 way and multiway SA. Results most sensitive to baseline risk of UGI event and cost of drugs.
The answer to the study question?	Cox IIs only cost effective only in patients with high baseline risk of UGI events.
Other issues	
Funding source	US Veterans Affairs
MI effects included?	No

Study: Spiegel et al. The cost-effectiveness of cyclooxygenase-2 selective inhibitors in the management of chronic arthritis. *Ann Intern Med* 2003;138(10):795-806

Study design	
The research question, including description of alternatives being compared	Patients with RA or OA with moderate or severe arthritic pain and without GI symptoms. Comparison of: - Cox II (either celecoxib or rofecoxib) - Nonselective NSAID (i.e. naproxen) Note: patients with history of ulcer complications considered as part of sensitivity analysis
The viewpoint(s) of the analysis	Third-party payer
The form of economic evaluation used	CUA
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	Systematic review and meta analysis of trials. Pooled estimate for cox IIs (i.e. both celecoxib and rofecoxib) derived
The primary outcome measure(s) for the economic evaluation	QALYs
Methods to value health states and other benefits, and subjects (if relevant)	Valuation method not stated. Utility estimates taken from single published source (Groeneveld et al, 2001)
Methods for the estimation of quantities and unit costs	Taken from routine health sector sources, including fee schedules and price lists
Currency and price data	US $ 2002
Details of any model used	Decision tree model (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	Lifetime
The discount rate(s)	3% for both costs and effects
Details of statistical tests	Monte Carlo simulation for PSA
Base case analysis results	See table below
Details of sensitivity analysis	1-way SA and probabilistic SA (assuming triangular distributions for all parameters) High-risk cohort modelled. Inclusion of cardiovascular events. "The coxib strategy became dominant when the cost of the coxibs was reduced by 90% of the current average wholesale price."
The answer to the study question?	In the management of average risk patients, coxibs are <u>not</u> CE but may provide an acceptable ICER in the subgroup of patients with a history of bleeding ulcers.
Other issues	
Funding source	US National Institute of Health and VA
MI effects included?	Yes, as part of SA

Study results

		Cost ($)	QALYs	ICER ($)
Base case	Naproxen	4859	15.2613	
	Coxib	16443	15.3033	275,800
Including cardiovascular events	Naproxen	2037	15.2539	
	Coxib	16620	15.2832	395,000
High-risk cohort (previous ulcer haemorrhage)	Naproxen	14294	14.7235	
	Coxib	19015	14.8081	55,800

Study: Rafter N et al. Listing rofecoxib and celecoxib in the Pharmaceutical Schedule. *PHARMAC Report* 2003

Study design	
The research question, including description of alternatives being compared	Comparison of Cox IIs (i.e. celecoxib and rofecoxib) and NSAIDs (i.e. ibuprofen, diclofenac). Looked separately at average risk population and high risk population (defined as those with previous UGI event) of patients with RA or OA.
The viewpoint(s) of the analysis	Health care sector
The form of economic evaluation used	CUA
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	CLASS trial – celecoxib VIGOR trial – rofecoxib plus other FDA sources
The primary outcome measure(s) for the economic evaluation	QALYs
Methods to value health states and other benefits, and subjects (if relevant)	Utility weights taken from range of published sources, including CCOHTA report
Methods for the estimation of quantities and unit costs	Routine health sector sources (e.g. N2 DRG costs) plus other published estimates
Currency and price data	NZ $, 2003
Details of any model used	Amended version of Maetzel model – Markov (diagram shown)
Analysis and interpretation of results	
Time horizon of costs and benefits	5 years
The discount rate(s)	10% in base case (? but not varied in SA?)
Details of statistical tests	None
Base case analysis results	Naproxen dominates rofecoxib Diclofenac dominates celecoxib Celecoxib vs ibuprofen: - ICER for average risk population: $482,000/QALY gained - ICER for high risk population: $88,000/QALY gained
Details of sensitivity analysis	1-way, 2-way and multiway SA performed. Only in extreme scenarios did celecoxib (vs ibuprofen) tend towards being CE.
The answer to the study question?	"Neither celecoxib nor rofecoxib provides sufficient incremental health benefits per dollar compared to NSAIDs to justify listing it on the New Zealand Pharmaceutical Schedule."
Other issues	
Funding source	Accident Compensation Corporation & Australasian Faculty of Public Health Medicine
MI effects included	Yes

Study: Maetzel et al. The cost effectiveness of Rofecoxib and Celecoxib in patients with osteoarthritis or rheumatoid arthritis. *Arthritis & Rheumatism* 2003;49(3):283-292

Study design	
The research question, including description of alternatives being compared	In average risk patients with RA or OA comparison of: - celecoxib vs diclofenac vs ibuprofen - rofecoxib vs naproxen In high risk patients with RA or OA comparison of: - rofeocoxib vs naproxen + PPI vs rofecoxib + PPI - celecoxib vs ibuprofen + PPI vs diclofenac + PPI vs celecoxib + PPI Note: 'high risk' defined as all patients who have a positive history of a clinical UGI event.
The viewpoint(s) of the analysis	Health sector perspective
The form of economic evaluation used	CEA and CUA
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	CLASS trial – celecoxib VIGOR trial – rofecoxib plus FDA sources
The primary outcome measure(s) for the economic evaluation	Clinical UGI event Complicated UGI event Life years QALYs
Methods to value health states and other benefits, and subjects (if relevant)	Study-specific SG utilities generated using 60 members of general public
Methods for the estimation of quantities and unit costs	Routine health sector and other published sources plus physician's focus groups
Currency and price data	Can $, 1999
Details of any model used	Markov model, developed by authors (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	5 years
The discount rate(s)	5% for both costs and QALYs
Details of statistical tests	None
Base case analysis results	See table below
Details of sensitivity analysis	Extensive 1-way on cost & QALY parameters. "rofecoxib would be cost saving at a price of approximately $0.33 per dose … and celecoxib would be cost saving … at a price of approximately $0.25 per 100mg twice per day".
The answer to the study question?	Prescribing of celecoxib and rofecoxib is only cost-effective in high risk patients.
Other issues	
Funding source	CCOHTA
MI effects included?	Yes

Study results

		Costs ($)	Complicated UGI events	QALYs	ICER (cost/QALY gained)
Average risk	Naproxen	1576	7.70	2.8938	
	Rofecoxib	3173	3.39	2.8997	271,000
	Ibuprofen	1141	6.36	2.8990	
	Diclofenac	2570	2.68	2.9104	125,000
	Celecoxib	3371	2.48	2.9095	Dominated by diclofenac
High risk	Rofecoxib	4090	7.45	2.8851	
	Naproxen + PPI	4766	11.31	2.8816	Dominated by rofecoxib
	Rofecoxib + PPI	6486	5.13	2.8936	281,000
	Celecoxib	4327	5.54	2.9003	
	Ibuprofen + PPI	4414	9.49	2.8894	Dominated by celecoxib
	Diclofenac + PPI	5980	4.11	2.9064	271,000
	Celecoxib + PPI	6746	3.81	2.9057	Dominated by diclofenac

Study: Kamath CC et al. The cost-effectiveness of Acetaminophen, NSAIDs, and selective COX-2 inhibitors in the treatment of symptomatic knee osteoarthritis. *Value in Health* 2003;6(2):144-157

Study design	
The research question, including description of alternatives being compared	For patients with symptomatic knee osteoarthritis (OA), comparison of: - rofecoxib - celecoxib - high dose acetaminophen ibuprofen (with or without misoprostol)
The viewpoint(s) of the analysis	Direct medical costs only
The form of economic evaluation used	CEA
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	For adverse GI events: Rofecoxib – Longman et al (1999), JAMA Celecoxib – CLASS And other relevant trials. For pain: FDA reviews and assumptions
The primary outcome measure(s) for the economic evaluation	Adverse events averted Achievement of minimally perceptible clinical improvement (MPCI)
Methods to value health states and other benefits, and subjects (if relevant)	N/A
Methods for the estimation of quantities and unit costs	Resource use and costs from billing data. (US) and assumptions
Currency and price data	US $, 2000 prices
Details of any model used	Decision tree model (diagram shown) (based on Maetzel model)
Analysis and interpretation of results	
Time horizon of costs and benefits	6 months
The discount rate(s)	N/A
Details of statistical tests	Monte Carlo simulation undertaken for PSA
Base case analysis results	See table below
Details of sensitivity analysis	1-way, 2-way and probabilistic SA performed "when effectiveness was defined as the number of GI events averted, ecetaminophen had the highest average net benefit in 100% of the Monte Carlo simulations."
The answer to the study question?	Acetaminophen dominates in terms of cost-GI event avoided. In terms of pain relief, only if one values pain relief above $14,150 if rofecoxib likely to be optimal.
Other issues	
Funding source	McNeil Consumer Healthcare (in part)
MI effects included?	No

Study results

	Cost ($)	AE averted	Pts achieving MPCI response
Acetomin	63,000	994.9	750
Ibuprofen	112,000	979.5	830
Rofecoxib	471,000	990.8	860
Celecoxib	474,000	990.3	790
Ibuprofen + misoprostal	556,000	987.7	830

Study: Bae SC et al. Cost-effective of low dose corticosteroids versus non-steroidal anti-inflammatory drugs and COX-2 specific inhibitors in the long-term treatment of rheumatoid arthritis. *Rheumatology* 2003;42:46-53

Study design	
The research question, including description of alternatives being compared	Main analysis: compared cortiosteroids and NSAIDs. Supplementary analysis: compared Cox II and cortiosteroids. Cox IIs considered: celecoxib and rofecoxib (not analysed separately) Patients with RA.
The viewpoint(s) of the analysis	Authors state that societal perspective considered but appears to be health sector only.
The form of economic evaluation used	Cost-utility analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	Strategies assumed to be equally effective. GI complications rate for cox II taken from published meta analysis (Goldstein et al, 1999)
The primary outcome measure(s) for the economic evaluation	QALYs
Methods to value health states and other benefits, and subjects (if relevant)	TTO and SG - QoL adjustments taken from variety of sources
Methods for the estimation of quantities and unit costs	Incidence of adverse events from meta analysis. Cost of treatment of AEs from variety of sources.
Currency and price data	US $, 1999
Details of any model used	Markov model – very few details given (no diagram)
Analysis and interpretation of results	
Time horizon of costs and benefits	Lifetime – for base case Patients 50 years at start of model
The discount rate(s)	3% for 'all values'
Details of statistical tests	None employed
Base case analysis results	See table below
Details of sensitivity analysis	For Cox II, only varied cost. "COX-2 inhibitors were superior to coticosteroids when the cost was less than $707."
The answer to the study question?	"Cortiosteroids are more cost-effective than NSAIDs and Cox II inhibitors in the long-term treatment of RA".
Other issues	
Funding source	Korean Ministry of Health & Welfare and Arthritis Foundation
MI effects included?	No

Study results

	Cost	QALYs	ICERs
Cortiosteroids	43,800	11.67	Cox II vs NSAID: $51,700
NSAIDs	44,900	11.46	Cox II vs cortiosteroid: $137,000
Cox II	63,000	11.81	

Study: Marshall JK et al. Incremental cost-effectiveness analysis comparing Rofecoxib with nonselective NSAIDs in Osteoarthritis. *Pharmacoeconomics* 2001;19(10):1039-1049

Study design	
The research question, including description of alternatives being compared	For patients with OA in whom paracetamol has failed, comparison of rofecoxib and non-selective NSAIDs
The viewpoint(s) of the analysis	Ontario Ministry of Health
The form of economic evaluation used	CEA
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	GI event rates taken from pooled analysis of 8 phase IIb/III clinical trials.
The primary outcome measure(s) for the economic evaluation	PUB avoided
Methods to value health states and other benefits, and subjects (if relevant)	Published and routine heath sector sources
Methods for the estimation of quantities and unit costs	N/A
Currency and price data	Can $, 1999
Details of any model used	Decision tree model (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	N/A
Details of statistical tests	None
Base case analysis results	ICER: $2,246 per PUB averted
Details of sensitivity analysis	Wide range of 1-way SA performed. Most SA scenarios still favour rofecoxib.
The answer to the study question?	"rofecoxib may represent a cost-effective alternative to nonselective NSAIDs."
Other issues	
Funding source	Merck
MI effects included?	No

Study: Pellissier JM et al. Economic evaluation of Rofecoxib versus nonselective nonsteroidal anti-inflammatory drugs for the treatment of Osteoarthritis. *Clinical Therapeutics* 2001; 23(7): 1061-1079

Study design	
The research question, including description of alternatives being compared	For osteoarthritis patients, comparison of rofecoxib and nonselective NSAIDs.
The viewpoint(s) of the analysis	Health sector
The form of economic evaluation used	CEA
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	GI event data taken from pooled analysis of rofecoxib trials.
The primary outcome measure(s) for the economic evaluation	PUB avoided. Life years gained.
Methods to value health states and other benefits, and subjects (if relevant)	N/A
Methods for the estimation of quantities and unit costs	Data taken from routine sources e.g. fee schedules, DRG costs etc.
Currency and price data	US $, 1998
Details of any model used	Decision tree model (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	N/A
Details of statistical tests	None
Base case analysis results	Base case: - cost/PUB avoided: $4,700 - cost/life year saved: $18,600 Adjustment for 'silent ulcers': rofecoxib is cost saving
Details of sensitivity analysis	Wide ranging 1-way SA Almost all scenarios explored gave a more favourable result for rofecoxib.
The answer to the study question?	"Costs per life year saved with rofecoxib versus NSAIDs were well within accepted benchmarks for cost-effectiveness."
Other issues	
Funding source	Merck
MI effects included?	No

Study: Chancellor JVM. Economic evaluation of Celecoxib, a new cyclo-oxygenase 2 specific inhibitor, in Switzerland. *Pharmacoeconomics* 2001; 19 Suppl 1: 59-75

Study design	
The research question, including description of alternatives being compared	For arthritis patients, comparison of: - celecoxib - NSAID plus H_2RA - NSAID along - NSAID plus misoprostol - NSAID plus PPI - diclofenac/misoprostol
The viewpoint(s) of the analysis	Health care sector
The form of economic evaluation used	Cost-consequence analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	GI event rates derived from pooled estimates from clinical trials.
The primary outcome measure(s) for the economic evaluation	GI events averted
Methods to value health states and other benefits, and subjects (if relevant)	N/A
Methods for the estimation of quantities and unit costs	Expert opinion for resource estimates. Routine sources for unit costs.
Currency and price data	Swiss Franc
Details of any model used	Decision tree model – Celecoxib outcomes measurement evaluation tool (COMET) (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	6 months
The discount rate(s)	N/A
Details of statistical tests	Monte Carlo simulation
Base case analysis results	Celecoxib associated with lowest cost and the fewest number of GI events, i.e. dominant therapy.
Details of sensitivity analysis	Probabilistic SA performed which confirmed dominance of celecoxib.
The answer to the study question?	"Celecoxib is predicted to be the most cost-effective of the treatments considered for managing arthritis patients in Switzerland."
Other issues	
Funding source	Pharmacia
MI effects included?	No

Appendix 8: Calculation of probabilities for initial cycle

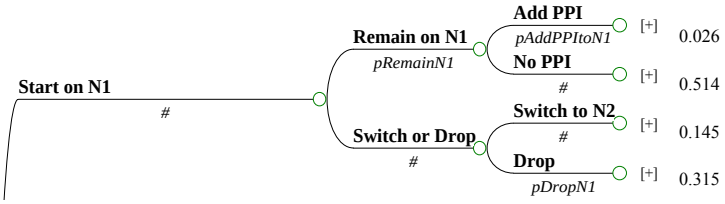
Table 93 was obtained by combining cells in Table 4 from Langman et al (ref).

Table 93: First and second prescriptions with and without GPDs among new patients

First prescription	Second prescription				
	No drug (%)	Same drug alone (%)	Different NSAID alone (%)	NSAID plus GPD (%)	Total
Ibuprofen alone	1059 (31.5)	1726 (51.4)	486 (14.5)	86 (2.6)	3357
Diclofenac alone	591 (26.5)	1342 (60.3)	213 (9.6)	80 (3.6)	2226

Consider the case where ibuprofen alone is the first line of treatment, the most likely course of action in primary care. Figure 30 shows four possible outcomes in Table 1. We have assumed that where patients are subsequently given an NSAID with a GPD a PPI is added: "Add PPI" in our model. We have also assumed that where patients are subsequently given a different NSAID this equates to "Switch to N2" in our model. The probabilities of reaching the various branches are as shown in the figure.

Figure 30: Changes from initial prescription



Then we have:

$$pRemainN1 = 0.026 + 0.514 = 0.540,$$
$$pAddPPItoN1 = 0.026/0.540 = 0.048,$$
$$pDropN1 = 0.315/(1 - 0.540) = 0.685.$$

(In the model, the probabilities for the outcomes are supplied as parameters and the probabilities in the tree are calculated by formulae corresponding to the calculations shown above.)

Appendix 9: Calculation of probabilities for main Markov cycles

The data for the model include risks of any GI event, clinical GI event, and complicated GI event. For ibuprofen and diclofenac, these are given as absolute risks. For COX-2 inhibitors, relative risks are given, compared to ibuprofen. Relative risks are also included for use of PPI and for previous GI event.

These are then combined to give probability of any GI event, probability of clinical GI event conditional on any GI event and probability of complicated GI event conditional on clinical GI event. For example, consider a patient on ibuprofen with PPI, post GI but not post MI.

The relevant risks are as shown below:

Baseline risks for "standard" patient	Risk (per year)
Risk of any GI event on ibuprofen	0.3115
Risk of clinical GI event	0.032
Risk of complicated GI event	0.0114
Relative risks to be applied	
PPI use (applies to all GI events)	0.4
Prior GI (applies to clinical and complicated GI events only)	2.6

These then convert to the following risks and probabilities:

Event	Risk (per year)	Probability of event occurring in 3-month cycle	Probability (conditional on previous event)
Any GI event	0.1246	0.0307	
Clinical GI event	0.0333	0.0083	0.2702
Complicated GI event	0.0119	0.0030	0.3572

(Results shown rounded but full accuracy maintained during calculations.)

Full calculations for clinical GI events (others are similar):

risk per year $0.032 \times 0.4 \times 2.6 = 0.0333,$

probability in cycle $1 - \exp(0.0333 \times 0.25) = 0.0083,$

probability conditional on any GI event $0.0083/0.0307 = 0.2702.$

The following probabilities are taken to be the same for all drugs:

Hospitalisation given complicated GI event	0.432
Surgery given hopitalisation	0.085
Death given complicated GI event	0.03

The justification for these is as follows:

Appendix 10: Univariate sensitivity analysis results

Varying relative risk of GI

Table 94: Results with relative risk for all types of GI event at the lower confidence limits (favouring COX-2 inhibitors)

Celecoxib (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£408.12		3.20925		
COX-2 Second	£475.82	£67.70	3.21084	0.00159	£42,700
COX-2 First	£915.86	£440.05	3.21739	0.00656	£67,100

Celecoxib (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£408.12		3.20925		
COX-2 Second	£562.89	£154.77	3.21084	0.00159	£97,500
COX-2 First	£1,527.69	£964.80	3.21739	0.00656	£147,000

Etodolac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£408.12		3.20925		
COX-2 Second	£450.29	£42.17	3.21132	0.00207	£20,400
COX-2 First	£740.99	£290.70	3.21960	0.00828	£35,100

Etoricoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£408.12		3.20925		
COX-2 Second	£473.63	£65.52	3.21321	0.00396	£16,500
COX-2 First	£904.79	£431.15	3.23271	0.01950	£22,100

Meloxicam (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£408.12		3.20925		
COX-2 Second	£423.30	£15.18	3.21185	0.00260	£5,830
COX-2 First	£549.57	£126.27	3.22389	0.01204	£10,500

Meloxicam (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£408.12		3.20925		
COX-2 Second	£439.08	£30.97	3.21185	0.00260	£11,900
COX-2 First	£660.48	£221.40	3.22389	0.01204	£18,400

Rofecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£408.12		3.20925		
COX-2 Second	£480.70	£72.58	3.21169	0.00244	£29,700
COX-2 First	£962.24	£481.54	3.22153	0.00984	£49,000

Valdecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£408.12		3.20925		

COX-2 Second	£473.74	£65.62	3.21245	0.00320	£20,500
COX-2 First	£908.08	£434.34	3.22703	0.01458	£29,800

Except where otherwise stated, ICER for each option is relative to the previous option listed. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY).

Table 95: Results with relative risk for all types of GI event at the upper confidence limits (favouring non-selective NSAIDs)

Celecoxib (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£476.43		3.19748		
COX-2 Second	£551.14	£74.71	3.19324	-0.00424	(Dominated)
COX-2 First	£999.15	£448.01	3.18795	-0.00530	(Dominated)

Celecoxib (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£476.43		3.19748		
COX-2 Second	£637.12	£160.69	3.19324	-0.00424	(Dominated)
COX-2 First	£1,603.47	£966.35	3.18795	-0.00530	(Dominated)

Etodolac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£476.43		3.19748		
COX-2 Second	£526.40	£49.97	3.19387	-0.00361	(Dominated)
COX-2 First	£825.86	£299.46	3.19242	-0.00145	(Dominated)

Etoricoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£476.43		3.19748		
COX-2 Second	£562.08	£85.65	3.19274	-0.00475	(Dominated)
COX-2 First	£1,062.63	£500.54	3.18880	-0.00393	(Dominated)

Meloxicam (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£476.43		3.19748		
COX-2 Second	£505.37	£28.94	3.19352	-0.00396	(Dominated)
COX-2 First	£674.94	£169.57	3.19046	-0.00306	(Dominated)

Meloxicam (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£476.43		3.19748		
COX-2 Second	£520.92	£44.49	3.19352	-0.00396	(Dominated)
COX-2 First	£784.20	£263.29	3.19046	-0.00306	(Dominated)

Rofecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£476.43		3.19748		
COX-2 Second	£561.32	£84.89	3.19198	-0.00550	(Dominated)
COX-2 First	£1,079.05	£517.73	3.17798	-0.01400	(Dominated)

Valdecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£476.43		3.197482		
COX-2 Second	£552.48	£76.05	3.195454	-0.00203	(Dominated)

COX-2 First	£1,012.84	£514.84	3.202347	0.00518	£110,000

ICER for "COX-2 First" relative to "No COX-2"

Except where otherwise stated, ICER for each option is relative to the previous option listed. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY).

Varying risk of MI

Table 96: Results with relative risk for MI at the lower confidence limits (favouring COX-2 inhibitors)

Celecoxib (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£510.61	£69.37	3.20374	-0.00054	(Dominated)
COX-2 First	£946.18	£504.93	3.20634	0.00206	£245,000

ICER for "COX-2 First" relative to "No COX-2"

Celecoxib (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£597.30	£156.06	3.20374	-0.00054	(Dominated)
COX-2 First	£1,555.34	£1,114.10	3.20634	0.00206	£540,000

ICER for "COX-2 First" relative to "No COX-2"

Etodolac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£485.04	£43.80	3.20445	0.00017	£257,000
COX-2 First	£770.83	£285.78	3.21018	0.00573	£49,900

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£441.25		3.20428		
COX-2 First	£770.83	£329.58	3.21018	0.00590	£55,900

Etoricoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£512.91	£71.66	3.20603	0.00176	£40,800
COX-2 First	£966.02	£453.11	3.22129	0.01525	£29,700

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£441.25		3.20428		
COX-2 First	£966.02	£524.78	3.22129	0.01701	£30,900

Meloxicam (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£462.95	£21.70	3.20466	0.00038	£57,200
COX-2 First	£612.30	£149.35	3.21242	0.00777	£19,200

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£441.25		3.20428		
COX-2 First	£612.30	£171.05	3.21242	0.00814	£21,000

Meloxicam (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER

No COX-2	£441.25		3.20428		
COX-2 Second	£478.66	£37.41	3.20466	0.00038	£98,600
COX-2 First	£722.70	£244.04	3.21242	0.00777	£31,400

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£441.25		3.20428		
COX-2 First	£722.70	£281.45	3.21242	0.00814	£34,600

Rofecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£519.07	£77.82	3.20431	0.00004	£2,110,000
COX-2 First	£1,015.43	£496.36	3.20877	0.00445	£111,000

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£441.25		3.20428		
COX-2 First	£1,015.43	£574.18	3.20877	0.00449	£128,000

Valdecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£511.27	£70.02	3.20560	0.00132	£52,900
COX-2 First	£957.89	£446.62	3.21758	0.01198	£37,300

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£441.25		3.20428		
COX-2 First	£957.89	£516.65	3.21758	0.01330	£38,800

Except where otherwise stated, ICER for each option is relative to the previous option listed. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY).

Table 97: Results with relative risk for MI at the upper confidence limits (favouring non-selective NSAIDs)

Celecoxib (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£514.30	£73.06	3.20320	-0.00108	(Dominated)
COX-2 First	£971.61	£457.31	3.20264	-0.00056	(Dominated)

Celecoxib (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£600.95	£159.70	3.20320	-0.00108	(Dominated)
COX-2 First	£1,580.48	£979.54	3.20264	-0.00056	(Dominated)

Etodolac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£488.76	£47.51	3.20391	-0.00037	(Dominated)
COX-2 First	£796.43	£355.18	3.20646	0.00219	£162,000

ICER for "COX-2 First" relative to "No COX-2"

Etoricoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£567.95	£126.70	3.19795	-0.00633	(Dominated)
COX-2 First	£1,345.61	£334.71	3.16555	-0.03240	(Dominated)

Meloxicam (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£466.66	£25.42	3.20412	-0.00016	(Dominated)
COX-2 First	£637.91	£196.67	3.20871	0.00444	£44,300

ICER for "COX-2 First" relative to "No COX-2"

Meloxicam (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£482.37	£41.12	3.20412	-0.00016	(Dominated)
COX-2 First	£748.26	£307.02	3.20871	0.00444	£69,200

ICER for "COX-2 First" relative to "No COX-2"

Rofecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£528.16	£86.92	3.20299	-0.00129	(Dominated)
COX-2 First	£1,078.14	£175.81	3.19962	-0.00336	(Dominated)

Valdecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.25		3.20428		
COX-2 Second	£512.70	£71.45	3.20539	0.00111	£64,100
COX-2 First	£967.74	£455.04	3.21614	0.01075	£42,300

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£441.25		3.20428		
COX-2 First	£967.74	£526.49	3.21614	0.01187	£44,400

Except where otherwise stated, ICER for each option is relative to the previous option listed. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY).

Testing the view that NSAIDs do not protect against MI

Table 98: Results with MI risk for No NSAID 0.23/100 person years – same as better non-selective NSAID (diclofenac)

Celecoxib (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£436.43		3.20497		
COX-2 Second	£506.96	£70.54	3.20426	-0.00071	(Dominated)
COX-2 First	£950.52	£514.09	3.2057	0.00072	£710,000

ICER for "COX-2 First" relative to "No COX-2"

Celecoxib (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£436.43		3.20497		
COX-2 Second	£593.63	£157.21	3.20426	-0.00071	(Dominated)
COX-2 First	£1,559.58	£1,123.15	3.2057	0.00072	£1,550,000

ICER for "COX-2 First" relative to "No COX-2"

Etodolac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER

No COX-2	£436.43		3.20497		
COX-2 Second	£481.40	£44.98	3.20497	-0.00001	(Dominated)
COX-2 First	£775.25	£338.82	3.20953	0.00456	£74,400

ICER for "COX-2 First" relative to "No COX-2"

Etoricoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£436.43		3.20497		
COX-2 Second	£510.45	£74.02	3.20638	0.00141	£52,700
COX-2 First	£978.47	£468.02	3.21946	0.01308	£35,800

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£436.43		3.20497		
COX-2 First	£978.47	£542.05	3.21946	0.01448	£37,400

Meloxicam (OA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£436.43		3.20497		
COX-2 Second	£459.31	£22.88	3.20518	0.0002	£112,000
COX-2 First	£616.71	£157.40	3.21178	0.0066	£23,900

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£436.43		3.20497		
COX-2 First	£616.71	£180.29	3.21178	0.0068	£26,500

Meloxicam (RA)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£436.43		3.20497		
COX-2 Second	£475.01	£38.59	3.20518	0.0002	£189,000
COX-2 First	£727.09	£252.08	3.21178	0.0066	£38,200

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£436.43		3.20497		
COX-2 First	£727.09	£290.67	3.21178	0.0068	£42,700

Rofecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£436.43		3.20497		
COX-2 Second	£516.93	£80.51	3.20462	-0.00036	(Dominated)
COX-2 First	£1,030.62	£594.19	3.20654	0.00157	£378,000

ICER for "COX-2 First" relative to "No COX-2"

Valdecoxib

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£436.43		3.20497		
COX-2 Second	£506.56	£70.14	3.20628	0.0013	£53,900
COX-2 First	£954.97	£448.40	3.218	0.01172	£38,300

Excluding the option "COX-2 Second" (by extended dominance):

No COX-2	£436.43		3.20497		
COX-2 First	£954.97	£518.54	3.218	0.01302	£39,800

Except where otherwise stated, ICER for each option is relative to the previous option listed. Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY).

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