

**THE CLINICAL EFFECTIVENESS AND COST
EFFECTIVENESS OF CELECOXIB, ROFECOXIB,
MELOXICAM AND ETODOLAC (COX-II INHIBITORS)
FOR RHEUMATOID ARTHRITIS AND
OSTEOARTHRITIS.**

On behalf of: The National Institute for Clinical Excellence

Report prepared by: NICE Appraisal Team

A number of unpublished studies were submitted as commercial in confidence. These data have been removed from this version of the assessment report to enable publication on the website. The Appraisal Committee had full access to these data prior to their meeting of 26th October 2000.

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EXECUTIVE SUMMARY

Background

Arthritis

Arthritis is a general term to describe the inflammatory disease of one or more joints, characterised by pain, swelling, stiffness, restriction of motion and redness of the skin overlying the affected joint. Osteoarthritis (OA) and rheumatoid arthritis (RA) are the two most common forms. Arthritis is very common, with an estimated number of OA patients around 1,325,000 – 1,750,000 and RA patients 250,000-500,000 in England and Wales.

Arthritis is an incurable disease, however control of inflammation, and associated symptoms can increase the quality of life and also delay the progression of the disease. Unlike for OA, there are some disease modifying drugs for RA. NSAIDs are widely used for the arthritis treatment due to their anti-inflammatory and analgesic effects, but with potentially significant gastrointestinal side effects. According to some estimates, around 2,000 deaths due to NSAID related side effects occur each year in the UK. Direct costs to NHS, including drug costs and health care resource use, are estimated to be around £300m annually.

Cox-II inhibitors

Cox-II inhibitors exert their action by selectively inhibiting Cox-II isoform of cyclooxygenase enzyme while sparing the effects on Cox I isoform, which is believed to play a role in maintaining gastrointestinal mucosal integrity. Therefore, theoretically Cox-II inhibitors should reduce the inflammation without causing GI side effects. There are four NSAIDs in the UK market with high claims of Cox-II selectivity including rofecoxib, celecoxib, meloxicam and etodolac. The degree of selectivity and also classification of these drugs remains controversial, mainly due to conflicting evidence from the range of different assays to assess selectivity.

Aims and Objectives

The aim of this review is to evaluate the clinical effectiveness and cost effectiveness of four Cox-II inhibitors (rofecoxib, celecoxib, meloxicam and etodolac) for the treatment of OA and RA, compared with other NSAIDs and also with each other.

Methods

A systematic review was conducted to include all published and unpublished randomised clinical trials, other systematic reviews, guidelines and economic evaluations. Information from industry, patient and professional groups' submitted to the Institute was also considered.

Results

Quantity and quality of evidence

The defined search strategy identified 673 articles relating to Cox-II inhibitors for arthritis, in addition to 15 abstracts identified from the company submissions. After scanning the titles and abstracts, 109 articles were obtained in full, and of those 63 papers met the inclusion criteria and were used in the clinical effectiveness review. There were no 'head to head' trials comparing Cox-II inhibitors with each other and most of the studies were small, therefore not adequately powered, and with heterogenous outcomes.

Three published economic evaluations were identified from the literature search. In addition to that, five economic modelling studies were identified, including four submitted by industry and two unpublished studies from the Canadian Coordinating Office for Health Technology Assessment (CCOHTA).

Clinical effectiveness evidence

- This review provides evidence that the Cox-II inhibitors (i.e. celecoxib, etodolac, meloxicam & rofecoxib) have equivalent efficacy to that of NSAIDs in terms of their ability to reduce pain and improve physical and global function of both OA and RA patients.
- There is evidence that the four Cox-II inhibitors are more effective in reducing the incidence of GI adverse events of OA and RA patients compared to NSAID therapy.
- There is no overall evidence to suggest that any of the Cox-II inhibitors included in this review is clinically superior to the others.
- Little or no subgroup analysis presented to that examines the impact of Cox-II inhibitors compared with NSAIDs in a high risk OA and RA patients.

Economic evidence

- There are few published cost-effectiveness studies and only one (meloxicam) study in the UK context.
- Economic evaluations submitted by the manufacturers report favourable cost per GI event averted and cost per life year gained (LYG) for all groups, with the exception of the submission by Shire. The upper range of cost per perforations, ulcers and bleeding (PUB) saved values in the industry submissions range between £3,500 to 10,759 and LYG values between £6,842 and £15,647... (in confidence)
- There are two cost per QALY estimates, both coming from Canadian studies... (in confidence)

- The results from different economic evaluations are less conflicting with favourable outcomes for high-risk groups, however definition of high-risk remains unclear.

Conclusions

- The effectiveness review found that the Cox-II inhibitors have equivalent efficacy to that of NSAIDs, but have less side effects. However, there is not enough evidence favouring any of the four drugs included in the review over the others.
- Although there is insufficient evidence in the literature to comment on the relative clinical effectiveness of the Cox II inhibitors in high-risk patients, the cost-effectiveness of Cox II inhibitors is likely to be more favourable for high-risk patients as the absolute number of gastrointestinal events averted would be greater in this group.
- The current evidence on cost-effectiveness of Cox II inhibitors remains inconclusive. There is need for methodologically sound cost-effectiveness trials, possibly using the data from “head to head” trials and in the UK context.

Abbreviations

ACR	American College of Rheumatology
ARA	American Rheumatism Association
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
COX	Cyclo-oxygenase
DMARDs	Disease modifying antirheumatic drugs
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GPA	Gastro-protective agents
H ₂ RA	Histamine 2 receptor antagonists
ICER	Incremental cost effectiveness ratio
LYG	Life-year gained
NNT	Number needed to treat
NSAID	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
PPI	Proton pump inhibitor
PUB	Perforation, ulcer and bleeding
QALY	Quality adjusted life years
RA	Rheumatoid arthritis
RR	Relative risk
UGI	Upper gastrointestinal
WBA	Whole blood assay
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WTP	Willingness to pay

1. Introduction

1.1. Aim of the review

The research question has been framed as to appraise the clinical effectiveness and cost effectiveness of the cyclooxygenase-2 (Cox-II) inhibitors for the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA). This study included rofecoxib, celecoxib, etodolac and meloxicam as non-steroidal anti-inflammatory drugs (NSAIDs), with claimed high Cox-II selectivity. The objective of the appraisal will be:

- to establish the clinical and cost effectiveness of the celecoxib and rofecoxib (coxibs) for the treatment of OA and RA, relative to etodolac and meloxicam;
- to establish the clinical and cost effectiveness of the Cox-II inhibitors for the treatment of OA and RA, relative to other NSAIDs.

1.2. Background

Description of underlying health problem

Arthritis is a general term to describe the inflammatory disease of one or more joints, characterised by pain, swelling, stiffness, restriction of motion and redness of the skin overlying the affected joint. Osteoarthritis (OA) and rheumatoid arthritis (RA) are the two most common forms of arthritis. Although the underlying mechanisms are distinct from each other, the former is thought to be degenerative in nature, the latter inflammatory. This paper will only cover OA and RA, as other arthritis types lie beyond the licence indications of the drugs in question¹.

1.3. Osteoarthritis (OA)

OA is a condition of the synovial joints characterised by cartilage loss with accompanying responses from bone around the joint. OA causes a major cause of morbidity and disability, especially for the elderly. It is the most common form of arthritis and may affect single or multiple joints. The most frequently affected joints are hands, knees, hip and spine. OA is a heterogenous disease for which the risk factors, pathophysiology, clinical features and outcomes vary depending on the joint involved. Therefore, the term "osteoartritic disorders" is suggested as a more appropriate label for the disease.

The aetiology of OA is not clear, but it is no longer regarded as a simple consequence of ageing and trauma (1). It is rather thought to be a result of both active inflammatory and reparative processes affecting cartilage in the joints (2). Most OA cases are idiopathic, however some may be secondary to other conditions that change the microenvironment of the chondrocyte, such

¹ Only meloxicam is also licensed for ankylosing spindylitis (please see Table 1.1).

as: congenital joint abnormalities; genetic defects; infectious, metabolic, endocrine, and neuropathic diseases; other bone and joint disorders (for example RA, avascular necrosis, gout, Paget's disease, chondrocalcinosis), and trauma.

Diagnosis and Classification

As OA represents a group of heterogenous conditions of multi-factorial aetiology, it may be "neither appropriate, desirable nor realistic" to define these conditions with a single set of criteria (3). Furthermore, most of the patients present with non-specific and highly subjective symptoms (such as poorly localised joint pain) and the diagnostic techniques are relatively insensitive to changes that occur during the natural course of the disease.

Diagnosis of OA is usually made by clinical examination and confirmed radiographically. The cardinal radiographic features are joint space narrowing and presence of bony spurs, called osteophytes. Most epidemiological trials are based on the presence radiographic features, although there are several other classifications available such as the ones developed by the American College of Rheumatology (ACR) based on clinical presentation. The degree of radiographic changes poorly correlates with clinical symptoms.

Most blood tests are normal in patients with uncomplicated OA, but may be helpful to rule out other causes of arthritis (e.g. gout, RA).

Epidemiology of osteoarthritis

Any estimates of overall prevalence of OA will be variable due to the differences in diagnostic criteria used in different studies (3). However, estimated prevalence of radiographically diagnosed OA in the UK is as high as 50% in the over 55 age group and most people over 65 years of age will have some radiological evidence of OA in at least one joint. Its prevalence rises with age, and is higher in women than in men.

The difference to overall prevalence of symptomatic OA is also not clear, but one study estimated that around 12% of over 65 year olds² are clinically affected (4), whereas others put the prevalence of symptomatic OA between 1.6 and 3.4 million in the over 45 year age group (5). Data from "4th Morbidity Statistics from General Practice" is shown in Appendix A. This data is now rather out-of-date, but applying the reported prevalence rates to 1997 England & Wales population figures yields an estimate of around 1,750,000 patients with OA. Arthritis and Rheumatism Council Epidemiology Unit estimates the prevalence of OA to be around 2,691 per 100,000 population (1,325,000 in England & Wales).

A recent cross-sectional study carried out in Avon and Somerset, involving 28,080 resident people aged 35 and over, has estimated the prevalence of self-reported hip pain as 107 per 1000 for men and 173 per 1000 for women

² That equates to around 1.15 million people in England & Wales

(6). The prevalence of hip disease severe enough to require surgery was calculated as 15.2 per 1000 aged 35-85 years. However the self-reported hip pain may not be an accurate proxy for the presence of OA and these figures may be overestimates³.

Estimates of the prevalence of symptomatic OA of knee also vary widely; between 6.1% - 28.7% of adult population (3).

Clinical Presentation

OA is a progressive disease with insidious onset. Symptoms include joint pain, morning stiffness, instability in the joint and loss of function. Joint pain can be mild to moderate during use of the affected joint, which normally eases with rest. Pain during the night or at rest is a sign of severe disease (1). Morning stiffness follows inactivity but lasts < 15 to 30 min and lessens with movement. Most commonly involved joints are the hands, feet, knees, and hips.

The natural history of OA is highly variable and clinical presentation depends on the site involved. As the disease progresses, loss of range of motion, tenderness and crepitus sensations (a crackling or grating sound) may appear. Proliferative changes in cartilage and bone or synovitis, or increased amounts of synovial fluid may cause the joint enlargement. Flexion contractures, muscle wasting and deformities develop in severe cases. Risk factors include advanced age, obesity, depletion of the sex hormones, and race/ethnicity. Environmental factors include the increased physical demands of work and leisure or sporting activities.

Management of OA

There is no known cure for OA or means of preventing it. Treatment of osteoarthritis is purely to control the symptoms of the disease and therefore usually revolves around controlling pain.

Non-drug treatment is considered as an initial therapy and it includes patient education, physical therapy (e.g. use of thermal modalities, transcutaneous electrical nerve stimulation (TENS), strengthening exercises), occupational therapy (e.g. joint protection and assistive devices), and weight loss programmes.

Pharmacological measures are used if non-drug treatment fails. The first drug of choice is usually paracetamol (1). NSAIDs are usually considered after the failure of these therapies. Intra-articular corticosteroids are widely used, especially as an adjunct in the treatment of knee and carpo-metacarpal OA. Surgical therapies, such as total knee/hip replacement and osteotomy, are considered as treatment options in severe cases.

³ Using these rates as proxy for OA of hip prevalence yields at least 4 million patients in England and Wales.

Outcome Measures

The most commonly used outcome measures used in the assessment of OA include patient and physician global assessments, frequency and severity of joint pain (at rest, with movement, pain intensity, night pain, weight bearing pain etc.) usually on VAS 0-100, stiffness (minutes or hours), functional impairment and disability. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a self-administered and disease-specific health status measure developed for the assessment of the patients with OA of the hip and/or knee. This index consists of 24 questions and probes clinically important symptoms in the areas of pain, stiffness and physical function. The Health Assessment Questionnaire (HAQ) is another method and measures difficulty in performing activities of daily living. It was initially designed for the clinical assessment of adult arthritics but has since been used in a wide range of research settings.

1.4. Rheumatoid arthritis (RA)

RA is the most common chronic inflammatory joint disease. It is a systemic auto-immune disorder and typified by widespread and persistent inflammation of the synovial lining of the (mainly peripheral) joints and tendon sheaths. Its course may extremely vary and is often associated with non-articular features.

Diagnosis and Classification

Diagnosis of RA usually clinical and based on number of criteria such as: symmetry of affected joints, morning stiffness, the presence of subcutaneous nodules and high serum rheumatoid factor (RF) levels. The revised classification criteria of the American Rheumatism Association (ARA) is given in Appendix B. Radiography may be used, especially in advanced disease, to determine the degree of joint destruction and to monitor disease progression. However, radiological findings early in the disease course may show nothing more than soft tissue swelling.

Unlike in OA, blood tests and serology is more informative in patients with RA. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are often elevated in proportion to the inflammatory process. RF is present in about 70% of the patients, although not pathognomonic. The anti-nuclear antibody (ANA) is also positive in 20-30% of patients with RA and is more common in patients with extra-articular manifestations. A blood test may reveal a normocytic-normochromic anaemia in some patients.

Aspiration of a joint which demonstrates effusion may also be useful, especially for the elimination of other conditions such as septic arthritis.

Differential diagnosis between osteoarthritis and rheumatoid arthritis can usually be made by the pattern of joints affected, and the absence in OA of systemic characteristics(7).

Epidemiology

The incidence of RA is estimated to be around 20-60/100,000. Due to the long duration of the disease, the prevalence is much higher, around 500-1000/100,000 (0.5-1%)(8). This translates into approximately 250,000 – 500,000 patients in England & Wales. Arthritis and Rheumatism Council Epidemiology Unit estimates the prevalence of RA to be around 1,241 per 100,000 population (610,000 in England & Wales), however this figure includes juvenile chronic arthritis and ankylosing spondylitis. Applying the GP Morbidity Statistics data (Appendix A) to 1997 England & Wales population figures, gives around 210,000 prevalent patients with RA, and 70,000 new cases each year.

Women before the menopause are affected three times more than men; after the menopause, the frequency of onset is similar between the sexes.

Clinical Presentation

Typically (in 70% of cases), RA manifests as slowly progressing, symmetrical, peripheral polyarthritis, which evolves over a span of a few weeks or months. However, in rapid-onset form of RA (15% of cases), severe symmetrical polyarthritis may develop over a few days (sometime explosively overnight), but surprisingly these cases have better prognosis (2). Symptoms include pain, swelling and stiffness of small joints in the hands and feet, but wrists, elbows, shoulders, knees and ankles can also be affected. Pain in the joints is worse in the morning but may improve with gentle activity, and patients often feel tired and unwell. Affected joints are usually warm and tender with some joint swelling due to the inflammatory activity. Bone destruction and permanent deformities may develop due to persistent inflammation as the disease progresses.

Extraarticular manifestations of RA include: rheumatoid nodules, Sjögren's syndrome, episcleritis and scleritis, interstitial lung disease, pericardial disease, systemic vasculitis, neuropathies, renal amyloidosis and Felty's syndrome, and usually indicate poor prognosis.

Management of RA

Optimal management of RA requires early diagnosis and treatment to control the underlying inflammatory process, and thereby to reduce the probability of irreversible joint damage. The aim of treatment is to reduce pain and stiffness, improving joint movement, minimising the loss of function and preventing deformities. Pharmacological treatment options include the analgesics, NSAIDs, disease-modifying drugs (i.e. sulfasalazin, methotrexate, penicillamine, gold compounds) and steroids. Education, dietary advice, physiotherapy and occupational therapy are the most commonly used non-drug management strategies. When the other treatment modalities fail to control the progression of the disease, surgery may be considered. The main surgical procedures are joint replacement, synovectomy and other minor interventions (i.e. carpal tunnel decompression, tendon release).

The “pyramid approach” in the treatment of RA, which involves the initial use of NSAID, then adding the disease modifying antirheumatic drugs (DMARDs) in stepwise fashion during the course of treatment, is no longer advocated. Early referral to a rheumatologist and treatment with DMARDs is shown to reduce the progression of joint damage.

Outcome Measures

The most commonly used outcome measures used in the assessment of RA include patient and physician global assessments, number of swollen or tender joints, pain score (usually on VAS), morning stiffness (minutes or hours), time to walk 50 feet, grip strength for both hands (mm/Hg), functional status, radiological progression, articular index, Ritchie’s index, changes in acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Comparative drug trials also utilise the rates of withdrawal from the treatment (due to both insufficient response and adverse effects), compliance, concomitant paracetamol consumption, global assessment of tolerability, endoscopically detected ulcer rates and also a variety of laboratory tests (liver function tests, urinalysis, complete blood count etc.) to evaluate the safety of the drug.

1.5. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are widely used in general practice for the treatment of musculoskeletal diseases due to their anti-inflammatory and analgesic effects, also representing one of the most commonly prescribed class of drugs in the UK. In 1999, over 18.5 million NSAIDs treatments were prescribed in England at a cost of approximately £170m⁴. There are over 40 different NSAIDs listed in the British National Formulary (BNF; see appendix C)(9). There is no clear evidence of substantial differences in efficacy between different NSAIDs, and therefore generally they are all accepted to be similarly efficacious. However, there is a considerable variation in the individual patient response and tolerance.

Mechanism of Action

All NSAIDs are believed to exert their action by interfering with the formation of prostaglandins (PG) from their precursor (arachidonic acid) via inhibiting the enzyme cyclooxygenase (Cox) which catalyses this process. PGs are responsible for mediating inflammation and pain, but they also play a critical role in protecting GI mucosa, supporting renal function, platelet activity and therefore haemostasis.

Side effects

The most common side effects associated with the use of NSAIDs are related to the GI system. These adverse effects range from mild dyspepsia to severe

⁴ 1999 Prescription Cost Analysis Data. This data does not include over the counter sales.

complications such as GI haemorrhage and perforation, and may lead to hospitalisation, surgery or even death, with important implications on both health care expenditure and on patient quality of life.

The presentation of symptoms may vary depending on the type of the NSAID, the dosage, duration of treatment and patient-related factors such as age, co-morbidity and current health status. In general, at least 10-20% of patients have dyspepsia while on NSAID treatment and 5-15% should be expected to discontinue within 6 months primarily due to GI adverse effects (10). Other side effects include renal dysfunction, hepatic dysfunction, dermatological reactions, and drug interactions.

Risk factors for NSAID related GI events

Advanced age is one of the major risk factors for drug-related GI events. Other identified risk factors include; higher doses of drugs, a history of GI disease or haemorrhage, serious co-existing conditions and concomitant use of steroids or anti-coagulants(10). A recent review, including 18 published studies, has shown that the risk of having upper GI tract bleeding (UGIB) increases steeply by age (up to 9.2 times in over 80 year olds compared with 25-49 year age group), with a further four-fold increase associated with NSAID use. Patients with previous complicated ulcer (bleeding or perforation) are reported to have the highest absolute risk (around 38.5) for UBIG (11). The VIGOR study(12)⁵ involving over 8,000 patients, has reported the relative risk of having a GI event as 4.0 for patients with prior UGI events and 2.5 for patients over 65 years of age.

It is difficult to clearly define the high-risk group patients and also estimate the overall proportion of them amongst all patients. However, several large studies reported that the proportion of OA patients with previous GI events is around 8% in clinical trial settings (13).

Use of Gastroprotective Agents (GPAs)

Gastroprotective agents are often co-prescribed with NSAIDs, with the aim to reduce the associated GI adverse effects. Co-prescribing rates range from 17 to 34% in the literature(14). The most commonly used GPAs include proton pump inhibitors (PPI), H₂ receptor antagonists (H₂RA) and misoprostol. Although these agents have shown to be efficacious to certain extent in prophylaxis and treatment of NSAID related GI events, they are not without additional side effects and they have cost implications to the NHS.

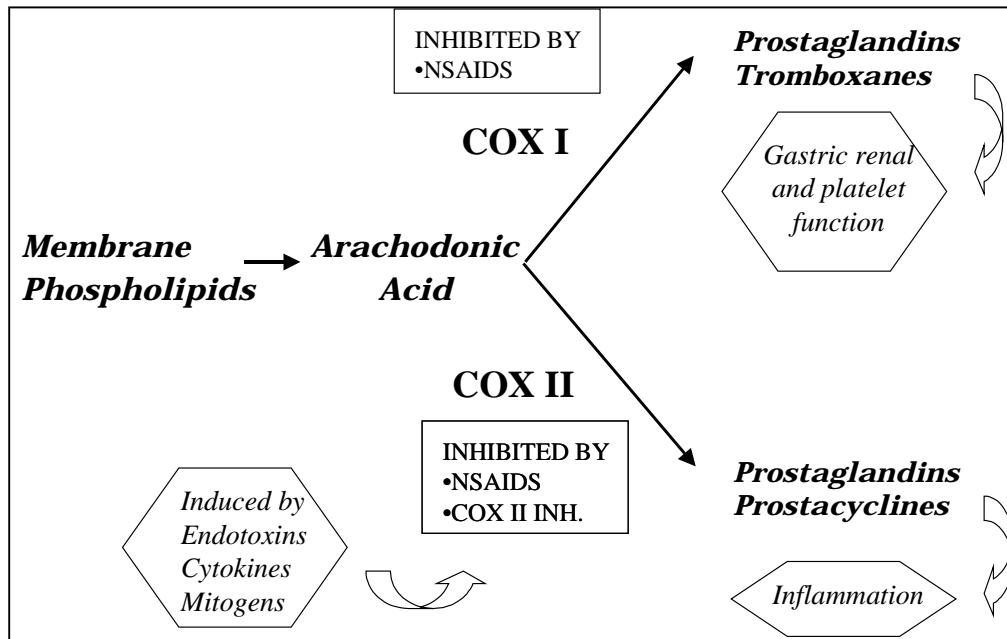
Misoprostol have shown to reduce the serious upper GI complications by almost 40%(15), but is poorly tolerated because of its own side effects, mainly diarrhoea and abdominal pain. Omeprazole is currently the only PPI licensed for both healing and prophylaxis of NSAID-associated ulcers, and usually better tolerated than misoprostol(16).

⁵ VIGOR study compared rofecoxib versus naproxen in over 8,000 patients. This study is currently in press.

1.6. Cox-II inhibitors

Recent data have shown that at least two isoforms of cyclooxygenase exist: Cox-I (constitutive enzyme) and Cox-II (inducible enzyme) and that different NSAIDs have different inhibitory profiles for these 2 isoforms (Figure 1).

Figure 1: Cyclooxygenase pathway



Cox I is found in platelets, vascular endothelial cells, stomach and kidney collective tubules in high concentrations, and is responsible for production of prostaglandins which are essential for maintenance of normal endocrine and renal function, gastric mucosal integrity and haemostasis. In contrast, Cox-II is virtually undetectable in most tissues under physiological conditions, but the enzyme activity may be dramatically up-regulated by inflammatory and mitogenic stimuli(17). These findings suggested that Cox-II plays a role in inflammation, while GI adverse effects may be due to the inhibition of Cox-I isoform. Traditional NSAIDs inhibit both Cox I and Cox-II, therefore the selective inhibition of Cox-II could prevent adverse events associated with NSAID use, while still maintaining the therapeutic anti-inflammatory properties.

Celecoxib and Rofecoxib (coxibs) are two recent Cox-II inhibitors, while there are several other NSAIDs with high Cox-II selectivity such as meloxicam and etodolac. Current licence indications of these drugs are given in Table 1.1. There is a considerable confusion and debate around the classification of Cox-II inhibitors and also the degree of Cox-II selectivity.

Table 1.1 Recommended daily dosage and license indications of Cox-II inhibitors (9) (for other licensed NSAIDs, see Appendix C)

Cox-II inhibitor	Recommended daily dose	Licence Indications
Rofecoxib	12.5-25 mg	Symptomatic relief in the treatment of OA
Celecoxib	200-400 mg	Symptomatic relief in the treatment of OA or RA
Meloxicam	7.5-15 mg	Short-term symptomatic treatment of acute exacerbations of OA long-term symptomatic treatment of RA symptomatic treatment of ankylosing spondylitis.
Etodolac	600 mg	acute or long-term treatment of RA or OA

Assessment of COX-2 selectivity

There are several types of assays that can be used to assess the Cox-II selectivity. Earlier in vitro assays that utilised animal enzymes or cell lines are no longer in use. In vitro human whole blood assay has become an accepted and reproducible standard (18), however it is often criticised for its inherent limitation that it may not truly reflect the Cox inhibition in target tissues (e.g gastric mucosa). The more recent in vitro assays are prepared by using human target cells such as gastric mucosal cells, chondrocytes and synoviocytes. Ex vivo assays measure the Cox-II selectivity by the relative inhibition of TXB₂ in monocytes and macrophages, platelet aggregation and renal PGE₂ synthesis

There are wide variations in ratios reported by using different assay techniques; therefore it is recommended that results from in vitro testing should only be used as a guide to the relative in vivo selectivity of different NSAIDs studied in the same assay system(19).

Selectivity for Cox-II enzyme is expressed by a ratio of Cox-II IC₅₀⁶ to the Cox I IC₅₀, that is less than 1. Thus, the lower the ratio, the greater the selectivity for Cox-II (20). These ratios may vary more than 100-fold for different NSAIDs (21). Some Cox-II selectivity ratios, reported in the literature, for selected NSAIDs are given in Table 1.2.

⁶ IC₅₀ (Inhibitory concentration 50%): the concentration of the NSAID needed to produce 50% inhibition

Table 1.2 Reported Cox-II selectivity for selected NSAIDs

NSAID	Reference				
	Feldman(21)	Warner et al(22)		Brooks et al(19)	Furst (23) WBA
		WBA ⁷	WHMA ⁸		
Aspirin	3.12	>100	4.4	2-167	
Piroxicam	0.79	3.3	0.1	9.4-600	0.3-12
Ibuprofen	1.69	0.9	2.6	0.67-53.3	2.0-6.1
Naproxen	1.79	3.0	3.8	0.6-75	0.4-9.5
Diclofenac	0.05	0.5	0.3	0.067-4	
Meloxicam	0.09	0.37	0.040	0.01-1.5	0.08-0.09
Etodolac	0.11	0.2	0.1		0.1
Nimesulide	0.04	0.19	0.038		
Rofecoxib ⁹	0.05	0.013	0.0049		0.004
Celecoxib ¹⁰	0.007	0.7	0.3		0.007

Classification

Classification of these drugs also remains controversial. Frequently, coxibs are classified as “Cox-II specific agents” and meloxicam and etodolac as “Cox-II selective”. In an international consensus meeting, “Cox-II specificity” was described as “inhibiting Cox-II, but not Cox I, in therapeutic dose range”. However, it was also stated that this definition does not imply that Cox-II specific drugs have an improved gastric safety profile, and that randomised controlled trials are still needed to establish the benefits of these new agents(19). This consensus meeting classified celecoxib and rofecoxib as “Cox-II specific” while mentioning meloxicam and nimesulide as “Cox-II preferential” agents. However, the controversy seems not to be resolved as some argue that the term “specific” should be used with exactitude in pharmacology and therefore may be inappropriate to define current Cox-II inhibitors (18). More recently “Cox I sparing NSAIDs” was suggested as an alternative name to describe this class of drugs. To remain out of this debate, the term “Cox-II inhibitors” will be used throughout this report to refer all those four drugs mentioned in research question.

1.7. Financial Implications

Economic Burden of Musculoskeletal Disorders

Musculoskeletal disorders form a major cause of morbidity and disability in the developed world and impose a considerable financial burden to both the NHS and patients. It is difficult to precisely quantify this burden, as these medical

⁷ WBA: Whole blood assay

⁸ WHMA: William Harvey human modified whole blood assay

⁹ In some cell lines expressing human Cox I and Cox-II, rofecoxib selectivity ratio could not be calculated as IC₅₀ for Cox I was undetectable for single doses up to 1000mg(119).

¹⁰ In some assays, celecoxib has shown to have no effect on whole-blood thromboxane B₂ activity(19). It is reported to be 375 fold selective for Cox-II (ratio: 2.67x10⁻³) in human recombinant enzyme assays(119).

conditions are complex and most patients are elderly with a number of co-morbid conditions. Musculoskeletal diseases are estimated to consume around 8% of all NHS and personal social services expenditure (24).

In 1986, March estimated the direct costs of arthritis (including hospital costs, GP costs and prescriptions) to be up to 1 billion pounds and stated that, assuming that indirect costs are three times the direct costs, the total economic burden would represent 1.1% of GNP (25). The NHS Executive has calculated the annual direct costs of OA to be £320m.

The NHS expenditure on the medical care for RA patients was estimated to be around £240m – £600m (26),(24). However, including the indirect costs, the overall cost of RA to society may be much higher, possibly between £0.8 and £1.3 billion per annum (8). In a recent review by Cooper(27), the mean annual direct costs associated with RA are estimated to be around £3,575 per patient. Overall average indirect costs were estimated to be at least as high (£3,638), whereas some studies included in the review reported indirect costs to be at least two to three times more than the direct costs.

Economic Burden of NSAID Related Side Effects

NSAID related side effects are common and they have major cost implications on the health services. According to prospective data from the Arthritis, Rheumatism and Aging Medical Information System (ARAMIS), collected from 2,747 patients with RA, the annual rate of hospitalisation due to GI event while taking NSAIDs was 1.6% compared with 0.3% in general population, with a relative risk ratio of 5.2. The gastrointestinal (GI) related death rate was also two-fold higher in RA patients taking NSAIDs (6% of deaths) compared with general population (3%)(28).

The risk of death due to NSAIDs over a lifetime may be substantial, mainly due to the large number of patients and extended duration of the treatment, although overall annual mortality may not be very high(10). Recently, Tramer et al estimated that on average one in 1,220 patients taking oral NSAIDs for 2 months or more will die from GI complications, which extrapolates to around 2000 deaths each year in the UK (29).

Moore et al estimate that the annual burden of NSAID-related GI side effects to the NHS is £251m - £367 m. This includes the direct hospital costs (£36m pa) and prophylactic co-prescriptions of PCA (£130m – £331m pa)(14).

2. Methods

2.1. Search Strategy And Bibliographic Databases Used

The following databases were searched for relevant literature (see Appendix D for search strategies) including systematic reviews.

- MEDLINE
- EMBASE
- Cochrane Controlled Trials Register (CCTR)
- National Research Register (NRR)
- NHS Economic Evaluation Database (NHS EED)
- Health Technology Assessment (HTA) database
- HEED
- Web searches for relevant systematic reviews or guidelines

The Cochrane Collaboration trial and CRD economic evaluation filters were used. The bibliographies of retrieved reviews were scanned for additional references.

The National Institute for Clinical Excellence approached the manufacturers (Boehringer Ingelheim, Pfizer & Searle, Shire and MSD) to submit any additional/unpublished data. These submissions were also scanned for relevant additional papers and abstracts.

The titles and abstracts identified by the searches were assessed, using an over inclusive approach so as not to miss potentially relevant reports. (see abstract selection table included in Appendix E.)

2.2. Inclusion and exclusion criteria

Studies were selected for inclusion in this review on the basis of the following.

Interventions

Cox-II inhibitors, celecoxib (Celebrex®), rofecoxib (Vioxx®), meloxicam (Mobic®) and etodolac (Lodine®) using the UK licensed daily dosage for each of the four drugs, i.e.

- celecoxib: 200-400mg (both RA & OA)
- rofecoxib: 12.5mg/25mg (OA only)
- meloxicam: 7.5mg (OA) & 15mg (RA)
- etodolac: 600mg (both RA & OA)

In the case of analysis of side adverse events (see below), studies with a licensed dose in excess of these doses were also included. Trials with doses lower than that the UK licensed dose were excluded.

Participants

Inclusion of patients presenting with rheumatoid arthritis (RA) or osteoarthritis (OA).

Study design

Studies that were systematic reviews, randomised controlled trials or economic analyses (cost-effectiveness, cost-minimisation, cost-utility or cost-benefit analysis) were sought.

Comparators

Trials that compared the study drugs with any other NSAIDs or placebo were included.

Outcomes

Outcomes related to the beneficial and adverse effects of the Cox-II inhibitors were sought.

Data extraction strategy

Data was extracted from the selected studies, using a prepared extraction form (see appendix F). Data extraction was carried out by one of the review team and checked for accuracy by another.

2.3. Assessment of study quality

The methodological quality of the included studies was assessed on the basis of the following criteria:

- Adequate concealment of randomisation
- Level of blinding
- Use of intention to treat analysis
- Proportion of patients lost to follow up

In addition, an overall quality score (Jadad) was assigned to each study, where possible. This score is based on the first three criteria above.

Methodological quality was assessed by one of the review authors and then independently checked by another.

2.4. Data presentation

For the clinical effectiveness part of this review, the effectiveness and adverse events components are presented separately.

Effectiveness

In order to assess overall efficacy, the results for each of the four drugs were presented separately for OA and RA patients.

Across the studies, a wide range of efficacy outcome measures were used, and as a lack of standardisation of outcome assessment reporting (i.e. pre- and post-treatment scores, change with treatment and percentage change with treatment) and inadequacy of this reporting of outcomes (i.e. measure of variance was often not provided), it was decided that it was inappropriate to statistically pool studies in terms of efficacy and the results. Therefore, the summary of efficacy results focuses on those trials with a sample size of ≥ 50 patients in each arm and a period of equal to or greater than four weeks.

Adverse events

Adverse event outcomes were combined across OA and RA studies since a causal relationship between the nature of the disease and adverse events related to treatment has not been demonstrated and the biological plausibility of such a relationship is low (30). The reporting of adverse outcomes was sufficient to allow pooling across studies to be performed (see below). The adverse outcomes were summarised under the following headings:

- Total number of adverse events reported
- Total number of gastrointestinal adverse events reported
- Total number of withdrawals through adverse events reported.
- Total number of perforations, ulcers or bleeding (PUB)

Separate comparisons were carried out for drug versus placebo and drug versus NSAID studies.

Data pooling

Study results were pooled using standard meta-analysis methods. The data are presented using a fixed effect model except in those circumstances where there was evidence of statistical heterogeneity, in which case the results were pooled using a random effects model. Results were selected for inclusion in pooling at the latest time point of a trial i.e. outcomes were separately reported at 2, 4 and 6 weeks then the 6 weeks results were used for pooling. All data analysis was undertaken using RevMan version 4.2.

3. Results: effectiveness of Cox-II inhibitors

3.1. Literature searches

The literature searches identified 673 articles relating to Cox-II inhibitors for arthritis. The titles and where available abstracts of the retrieved references were scanned and it was agreed that 109 would be obtained in full. A further 15 papers [abstracts] were identified from the company submissions (30-33).

On closer examination of the full papers a number were rejected on the basis that they did not meet the inclusion criteria.

No systematic reviews covering the Cox-II inhibitors for arthritis were found. Two Cochrane reviews on NSAIDs for osteoarthritis of the knee (4) and osteoarthritis of the hip (34) were retrieved.

The number of publications in the table below includes duplicate trials (where a trial has been published in abstract and full form). Some papers used both other NSAIDs and placebo as comparators and therefore appear twice in these figures. See Appendix G for a list of excluded studies

Table 3.1 Efficacy papers on Cox-II inhibitors

Drug	Indication	No of papers	Comparator	No. of trials (per comparator)	Trials meeting effectiveness criteria
Celecoxib	OA	7	vs. placebo	5	4
			vs. NSAIDs	2	
	RA	5	vs. placebo	1	3
			vs. NSAIDs	2	
	OA & RA	4	vs. placebo	2	0 (all measuring a.e.only)
			vs. NSAIDs	3	
Rofecoxib	OA	10	vs. placebo	8	7
			vs. NSAIDs	7	
	RA	2	vs. placebo	1	2
			vs. NSAIDs	1	
Meloxicam	OA	9	vs. placebo	2	7
			vs. NSAIDs	8	
	RA	2	vs. placebo	1	0
			vs. NSAIDs	2	
Etodolac	OA	3	vs. placebo	0	2
			vs. NSAIDs	3	
	RA	20	vs. placebo	6	3
			vs. NSAIDs	19	

3.2. Included studies

The following tables detail the study characteristics for the included studies for both effectiveness and adverse events analysis.

Table 3.2 Celecoxib for Rheumatoid arthritis

TRIAL	Emery, 1999 (35); Geis, (36)	Simon, 1999 (37), Geis (38)	Simon, 1998 (39)
Intervention	2 x 200mg/day	2 x 100mg or 2 x 200mg or 2 x 400mg celecoxib per day	2 x 40 or 2 x 200 or 2 x 400mg/day celecoxib
Control	2 x 75mg diclofenac SR	2 x 500mg naproxen or placebo	placebo
Country	various	U.S. & Canada	U.S.
No. of patients	655	1149	330
% female Interven-tion(s) Control	73.5	74/73/72 72, 73	77.6
Mean age Interven-tion(s) Control	55.9 54.5	54/55/54 55, 54	55.6, 55.5, 56.7 56.5
Outcomes	Global assessments; tender or painful joints; swollen joints; pain score (VAS); morning stiffness; MHAQ fd index; GI effects, ulcers, erosion	ACR-20 responders index; global assessments; tender & painful joints; swollen joints; arthritis pain VAS; HAQ functional disability index; morning stiffness' GI, renal and other adverse effects	Patient global assessments; tender/painful joints; pain assessment (VAS); composite assessments
Quality	24 week, double-blind, double-dummy, randomised, parallel	12 week, double-blind, randomised, Multicentre, placebo controlled	4 week double-blind randomised
Jadad score	4	4	2
Included in efficacy analysis	yes	yes	yes

Table 3.3 Celecoxib for osteoarthritis

TRIAL	Simon 1998 (39)	Bensen, 1999 (40), Hubbard, 1999 (41) Zhao, 1999 (42)	Geis, 1999 (43)	Williams, 2000 (44) Zhao,1999 (45)
Intervention	2 x 40 or 100 or 200mg/day celecoxib	2 x 50mg/day or 2 x 100mg/day or 2 x 200mg/day celecoxib	2 x 50 or 100 or 200mg/day celecoxib	2 x 100mg/day or 2 x 200mg/day celecoxib
Control	placebo	2 x 500mg/day naproxen or placebo	2 x 500mg/day naproxen	placebo
Country	U.S.	U.S. & Canada	U.S.	U.S.
No. of pts. (total)	293	1003	1053	686
% female (total)	68.9	72	n/s	66.5
Mean age Intervention(s) Control	60.9, 63.0, 61.9 61.3	62,62,63 62, 62	n/s	63.0, 62.7 62.6
Outcomes	Patient global assessments; pain assessment (VAS); adverse effects	Global assessments; SEM WOMAC OA Index scores; SEM OA severity index; pain measures; GI, renal and other adverse effects	Global assessments, pain assessments (VAS); OA severity index	Global assessments; arthritis pain; WOMAC OA, OA severity index; GI and other adverse effects
Quality	2 week double-blind, randomised	12 week double-blind, randomised, multi-centre, parallel	12 weeks double-blind, randomised	6 week double-blind, randomised, multicentre
Jadad score	4	3		3
Included in effectiveness analysis?	no	yes	yes	yes

Table 3.4 Celecoxib for rheumatoid arthritis and osteoarthritis

TRIAL	Silverstein, 2000 (46) CLASS study	Burr, 1999 (47)	Bensen, (48)	Hubbard, 1998 (49)
Intervention	2 x 400mg/day celecoxib	2 x 200mg/day celecoxib	2 x 50 or 100 or 200 or 400mg/day celecoxib	2 x 40 or 100 or 200mg/day celecoxib
Control	3 x 800mg ibuprofen OR 2 x 75mg/day diclofenac	2 x 500mg/day naproxen	2 x 500mg/day naproxen or placebo	Placebo
Country	U.S. & Canada	n.s.		U.S.
No. of pts. (total)	8059	536	5617 (5 trials)	n.s.
% female (total)	68.8	n.s.	n.s.	n.s.
Mean age Intervention(s) Control	60.6 59.8	n.s.	n.s.	n.s.
Outcomes	GI adverse events; bleeding, gastric or duodenal perforation, outlet obstruction.	Gastric and duodenal erosions or ulcerations	Adverse effects: dyspepsia; abdominal pain; nausea	Global assessments; pain; OA severity index; morning stiffness; GI adverse effects
Quality	6 month, double-blind, randomised, multicentre	12 week, double-blind, randomised, controlled	12 week, double-blind, parallel, randomised	Double-blind,
Jadad score		Not calculable		Not calculable
Included in effectiveness analysis?	No	No	No	no

Table 3.5 Rofecoxib for rheumatoid arthritis

TRIAL	<u>Bombardier, 2000 (12)</u> <u>Confidential (VIGOR trial)</u>	<u>Schnitzer, 1999 (50)</u>
Intervention		5 or 25 or 50mg/day rofecoxib
Control		Placebo
Country		U.S.
No. of pts. (total)		658
% female (total)		76.9
Mean age Interven-tion(s) Control		54.8, 55.7, 54.4 54.7
Outcomes		Tender or swollen joints; global assessments; SHAQD index; various adverse effects
Quality		8 week, double-blind, randomised, multicentre
Jadad score		3
Included in efficacy analysis		yes

Table 3.6 Rofecoxib for osteoarthritis

TRIAL	Saag, 1998 (51)	Truitt, 1999 (52)	Hawkey, 2000 (53)	Cannon, 2000 (54)	Day, 2000 (55;56)
Intervention	12.5mg or 25mg rofecoxib	12.5 or 25mg/day rofecoxib	25 or 50mg/day rofecoxib	12.5 or 25mg/day rofecoxib	12.5 or 25mg/day rofecoxib
Control	800mg/day ibuprofen or placebo	1500mg/day nabumetone or placebo	3 x 800mg/day ibuprofen or placebo	3 x 50mg/day diclofenac	3 x 800mg/day ibuprofen or placebo
Country		U.S.	various	U.S.	various
No. of pts. (total)	736	341	775	784	809
% female (total)	n.s.	n.s.	74.5	67.5	80.9
Mean age Intervention(s) Control	n.s.	(total) 83	62, 61 61, 62	62.8, 62.8 62.5	64.9, 62.8 64.1, 63.1
Outcomes	WOMAC pain on walking scale	Global assessments; WOMAC OA index; disease status	GI adverse effects; ulcers, erosions and other	Pain on walking; global assessments; WOMAC index; joint tenderness; adverse effects	Pain on walking; global assessments; WOMAC index; pain, stiffness and tenderness in joints
Quality	6 week double-blind, randomised	6 week double-blind, randomised, Multicentre	24 week blinded, randomised, multicentre	One year, double-blind, randomised, multicentre	6 week double-blind, randomised, multicentre
Jadad score	Not calculable	Not calculable	5	4	3
Included in efficacy analysis	yes	yes	no	yes	yes

Rofecoxib for osteoarthritis (cont'd)

TRIAL	Geba, 1999 (57)	Laine, 1999 (58)	Ehrich, 1997 (59)	Ehrich, 1999 (60)
Intervention	12.5mg/day rofecoxib	25 or 50mg/day rofecoxib	5 or 12.5 or 25 or 50mg/day rofecoxib	25 or 125mg/day rofecoxib
Control	1000mg/day nabumetone or placebo	3 x 800mg/day ibuprofen or placebo	Placebo	Placebo
Country	U.S.	U.S.	U.S.	U.S.
No. of pts. (total)	1042	742	672	219
% female (total)	n.s.	67.5	n.s.	71.2
Mean age Intervention(s) Control	(total) 63	62, 62 62, 61	n.s.	64.0, 63.9 62.6
Outcomes	Global assessments	GI adverse effects, ulcers, erosions, etc.	Global assessments; WOMAC pain when walking;	Global assessments; WOMAC scales, pain scales, various adverse effects
Quality	6 week, double-blind, randomised	6 month, double-blind, randomised	6 week double-blind, randomised, Multicentre	6 week double-blind, randomised, multicentre
Jadad score	Not calculable	5	Not calculable	5
Included in effectiveness analysis	yes	no	yes	yes

Table 3.7 Meloxicam for rheumatoid arthritis

TRIAL	Wojtulewski, 1996 (61)	Lemmel, 1997 (62)
Intervention	7.5mg/day meloxicam	7.5mg or 15mg/day meloxicam
Control	3 x 250mg/day naproxen	Placebo
Country	Various	Various
No. of pts. (total)	379	468
% female (total)	n.s.	n.s.
Mean age Intervention(s) Control	n.s.	53.6, 55.2 55.3
Outcomes	Global assessments; grip strength; swollen joints; painful/tender joints; morning stiffness; ESR; pain in morning; pain at night; adverse effects, GI and others	Disease activity; painful/tender joints; swollen joints; global assessments; health questionnaire; grip strength; morning stiffness; ESR; adverse events
Quality	26 week, double-blind, randomised, Multicentre	21 day, double-blind, randomised, multi-centre
Jadad score	3	2
Included in effectiveness analysis	no	no

Table 3.8 Meloxicam for osteoarthritis

TRIAL	Lund, 1998 (63)	Yocum, 1999 (64)	Linden, 1996 (65)	Hosie, 1996 (66)	Hosie, 1997 (67)	Goei The, 1997 (68)
Intervention	7.5mg or 15mg/day meloxicam	3.75mg or 7.5mg or 15mg/day meloxicam	15mg/day meloxicam	7.5mg/day meloxicam	15mg/day meloxicam	15mg/day meloxicam
Control	Placebo	2 x 50mg diclofenac or placebo	20mg/day piroxicam	100mg/day diclofenac SR	20mg/day piroxicam	100mg/day diclofenac SR
Country	Various European	U.S.	Various	U.K.	U.K.	Belgium, Denmark, Germany, Netherlands
No. of pts. (total)	411	774	256	336	455	258
% female (total)	72.7	n.s.	62.9	58.9	57	83.7
Mean age Intervention(s) Control	69.5, 67.9 68	n.s.	67.2 67.2	64.3 64.2	65.5 64.0	71.5 71.4
Outcomes	Pain on movement, pain at rest, index of severity, global efficacy, adverse events	WOMAC scale; pain, global assessments; GI adverse events	Pain on movement; pain at rest; global assessment; GI and other adverse effects	Overall pain, pain on movement; global assessments; duration of stiffness; quality of life profile	Overall pain; pain on movement; duration of stiffness; adverse effects including GI and others	Pain on movement; worst pain at rest; index of severity; global assessments; adverse effects
Quality	3 week, double-blind, randomised, Multicentre	12 week, double-blind, randomised, double-dummy, parallel	6 week, double-blind, randomised, multicentre	6 month, double-blind, randomised, multicentre	Six month, double-blind, randomised, multicentre	6 week, double-blind, randomised, multicentre
Jadad score	3	Not calculable	3	3	3	3
Included in effectiveness analysis	no	yes	yes	yes	yes	yes

Meloxicam for osteoarthritis (cont'd)

TRIAL	Valat, 1998 (69)	Hawkey, 1998 (70)	Dequeker, 1998 SELECT trial (71)
Intervention	7.5mg/day meloxicam	7.5mg/day meloxicam	7.5mg/day meloxicam
Control	100mg/day diclofenac SR	100mg/day diclofenac SR	20mg/day piroxicam
Country	various European	Various	various
No. of pts. (total)	229	9323	8656
% female (total)	82.5	66.9	67.5
Mean age			
Intervention(s)	58.5	61.5	61.3
Control	57.9	61.7	61.6
Outcomes	Pain score on movement; pain at rest; lateral mobility; sagittal mobility; global efficacy; adverse events	Adverse events; GI disorders (dyspepsia, nausea, vomiting, abdominal pain, diarrhoea); CNS, skin, urinary, etc.	Adverse events; GI disorders (dyspepsia, nausea, vomiting, abdominal pain, diarrhoea, ulcers)
Quality	14 day, double-blind, double-dummy, randomised, parallel group	4 week, double-blind, double-dummy, randomised, multicentre	4 week, double-blind, double-dummy, randomised, multicentre
Jadad score	Not calculable	3	3
Included in effectiveness analysis	no	yes	yes

Table 3.9 Etodolac for rheumatoid arthritis

TRIAL	Vetter, 1982 (72)	Jacob, 1983 (73)	Gordon, 1983 (74)	Del Toro, 1983 (75)
Intervention	LOW – 2 x 25 or 50 or 100mg/day HIGH – 2 x 100, 200 or 300mg/day	100-400mg/day etodolac	Titrated levels of etodolac (100, 200, 300, 400mg/day)	(100, 200, 300, 400mg/day)
Control	placebo	3600-4800mg/day aspirin or placebo	Titrated levels of aspirin (3600, 4000, 4400, 4800mg/day) or placebo	3600 - 4800mg/day aspirin or placebo
Country	U.S.	U.S.	U.S.	Puerto Rico
No. of pts. (total)	24	194	25	21
% female (total)	58.3	70	88	66.7
Mean age	58.6/58.5	50.4	54	48
Interven-tion(s)	62.3/58.5	52.0, 53.2	58, 55	50, 57
Control				
Outcomes	Painful joints; swollen joints; articular index; pain intensity; grip strength; morning stiffness; walking time; ESR; pain intensity; patient self assessment; side effect complaints	Pain intensity; articular index, no. of painful joints; no. of swollen joints; ESR; morning stiffness; grip strength; walking time; global assessments; GI and non-GI adverse events	No. of painful joints; no. of swollen joints; articular index; pain intensity; grip strength; morning stiffness; ESR; global assessments; GI, CNS, dermatological and other adverse events	Painful joints; swollen joints; articular index; pain intensity; grip strength; morning stiffness; walking time; ESR; GI, hepatic, CNS, dermatological side effects
Quality	4 week double-blind, randomised, parallel group	12 week, double-blind, parallel group, multicentre.	14 week, double-blind, parallel group	12 week, double-blind, parallel, randomised
Jadad score	3	3	2	3
Included in effectiveness analysis	no	no	no	no

Etodolac for rheumatoid arthritis (cont'd)

TRIAL	Edwards, 1983 (76)	Jacob, 1986 (77)	Jacob 1985 (78)	Waltham-Weeks, 1987 (79)	Taha, 1989 (80)
Intervention	100-400mg/day etodolac	50mg or 100mg or 200mg of etodolac per day.	Titrated doses of etodolac between 300-600mg/day	2 x 200mg/day etodolac	2 x 300mg/day etodolac
Control	Titrated levels of aspirin or dummy	3900mg/day aspirin or placebo	Titrated levels of aspirin to 4800mg/day	2 x 500mg/day naproxen	2 x 500mg/day naproxen
Country	U.S.	U.S.	U.S.	U.K.	U.K.
No. of pts. (total)	18	264	475	39	30
% female (total)	50	60.2	74	59	70
Mean age Intervention(s)	51	52, 54, 52	49	51.6	50
Control	55, 55	53, 53	49	55.6	57
Outcomes	Painful joints; swollen joints; articular index; pain intensity; grip strength; morning stiffness; walking time; ESR; GI, hepatic, CNS, dermatological side effects	No. of painful joints; no. of swollen joints; morning stiffness; average grip strength; walking time; opinion of condition; patient self- evaluation; pain intensity; articular index; ESR; ADVERSE EFFECTS patient complaints.	Painful joints; swollen joints; morning stiffness; grip strength; walking time; patient self assessment; pain intensity; articular index, ESR; GI, metabolic, CNS and other adverse effects.	Painful joints, swollen joints; articular index; morning stiffness; pain intensity; grip strength; ESR, global evaluation	Morning stiffness; grip strength; articular index; ESR
Quality	12 week, double blind, parallel group, randomised	6 week, double-blind randomised, multicentre	51 week, double-blind, randomised, Multicentre	14 week, randomised, double-blind, cross-over	4 week, double-blind, randomised, parallel group, single centre
Jadad score	3	3	4	3	3
Included in effectiveness analysis	no	no	yes	no	no

Etodolac for rheumatoid arthritis (cont'd)

TRIAL	Ciampi, 1989 (81)	Taha, 1990 (82)	Porro, 1991 (83)	De Queiros, 1991 (84)	Schattenkirchner, 1991 (85)	Briancon, 1991 (86)
Intervention	3 x 200mg/day etodolac	2 x 300mg/day etodolac	2 x 200mg/day etodolac	2 x 200mg/day etodolac	2 x 200mg/day etodolac	2 x 200mg/day etodolac
Control	3 x 150mg/day diclofenac	2 x 500mg/day naproxen	2 x 500mg/day naproxen	2 x 500mg naproxen	20mg/day piroxicam	20mg/day piroxicam
Country	Italy	U.K.	Italy	Portugal	Germany	France
No. of pts. (total)	16	27	48	39	60	40
% female (total)	75	70.4	90.0	87.2	77	85
Mean age		(median)	(median)			
Intervention(s)	63.5	50	52.7	46	56.1	54.8
Control	59.9	60	48.1	47	52.8	56.5
Outcomes	Richie Index; grip strength AUC; laboratory data	Morning stiffness; grip strength; articular index, ESR; gastric and duodenal prostaglandins	Pain; morning stiffness; Ritchie index; grip strength; laboratory data; endoscopic evaluations	Tender joints; swollen joints; global evaluation; pain intensity; grip strength; morning stiffness; ESR	Painful joints; swollen joints; pain intensity; global assessments; morning stiffness; grip strength; walking time; patient complaints	Painful joints; swollen joints; morning stiffness; walking time; ARA functional class; global evaluations; pain intensity; patient complaints
Quality	14 day double-blind randomised cross-over	4 week double-blind randomised	4 week, double-blind, randomised, double-dummy	12 week double-blind randomised	12 week, double-blind, randomised, parallel, single centre	12 week, double-blind, multicentre, randomised, parallel
Jadad score	2	2	3	3	3	3
Included in effectiveness analysis	no	no	no	no	no	no

Etodolac for rheumatoid arthritis (cont'd)

TRIAL	Porzio, 1993 (87)	Carson Dick, 1993 (88)	Lonauer, 1993 (89)	Lightfoot, 1997 (90)	Neustadt, 1997 (91)
Intervention	600mg/day etodolac SR	2 x 200mg/day etodolac	2 x 200mg/day etodolac	LOW: 200mg/day bid etodolac HIGH: 300mg/day bid etodolac	LOW: 2 x 150mg/day etodolac HIGH: 2 x 500mg/day etodolac
Control	100mg/day diclofenac	20mg/day piroxicam	150mg/day diclofenac	4 x 20mg/day piroxicam	4 x 600mg/day ibuprofen
Country	Germany, Italy	U.K., Belgium	Germany, Netherlands	U.S. & Europe	U.S.
No. of pts. (total)	91	118	108	426	1446
% female (total)	83.5	74	66.6	71.3	70.6
Mean age					
Intervention(s)	58	54.1	58.3	57/58	53.2/53.0
Control	55	54.6	57.5	56	53.1
Outcomes	Painful joints; swollen joints; global assessments by physician and patient; pain; morning stiffness; grip strength; walking time; articular index; ESR	Tender joints; swollen joints; morning stiffness; patient evaluation; pain intensity;	Global assessments; painful joints; swollen joints; pain intensity; grip strength; morning stiffness.	Global assessments; painful joints; swollen joints; pain intensity; articular index, grip strength; ESR; morning stiffness	Swollen joints; patient/ investigators opinions; side effects; GI ulcers and bleeding
Quality	4 week, double-blind, randomised, parallel	12 week, double-blind, parallel, randomised, multicentre	12 week, double-blind, randomised, multicentre	12 week, double blind, parallel, randomised, multicentre	3 year, double-blind, randomised, parallel, multicentre
Jadad score	3	3	2	3	2
Included in effectiveness analysis	no	no	no	yes	yes

Table 3.10 Etodolac for osteoarthritis

TRIAL	Chikanza, 1994 (92)	Perpignano, 1994 (93)	Rogind, 1997 (94)
Intervention	2 x 300mg/day etodolac	600mg/day etodolac	600mg/day etodolac
Control	2 x 500mg/day naproxen	20mg/day tenoxicam	20mg/day piroxicam
Country	UK	Italy	Denmark
No. of pts. (total)	76	120	271
% female (total)	77.6	88.3	78.7
Mean age	(median		
Intervention(s)	61	70.4	67.0
Control	63	71.0	67.5
Outcomes	Early morning pain; weight-bearing pain; adverse events,	PVAS; PAM; night pain; joint tenderness; joint motility; Lequesne score; patient and investigator overall assessment; erosive or haemorrhagic GI lesions	Patient assessment; investigator assessment; pain at rest; weight bearing pain; morning stiffness GI and non GI adverse events
Quality	9 week, double-blind, randomised ,crossover study, multicentre	8 week, double-blind, double-dummy, randomised, multicentre	8 week, double-blind, double-dummy, randomised, multicentre
Jadad score	3	3	3
Included in effectiveness analysis	no	yes	yes

Results of trials selected for inclusion in the beneficial effects analysis

KEY TO TABLES: N = number of patients; Oms= outcome measures; SS= statistically significant; LOE= lack of efficacy; yoa= years if age; DMARD=disease modifying antirheumatic agent; CCX= corticosteroids; GCX= glucocorticoids; MTX= methotrexate; * = 100mm Visual Analogue scale

Table 3.11 Celecoxib

Celecoxib vs. placebo: osteoarthritis

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
Bensen 1999 (40-42;49;95) celecoxib 50mg/bd or 100mg/bd or 200mg/bd placebo N=805, 12 weeks, knee ARC functional class I-III no concomitant >18 yoa aspirin and paracetamol rescue	patient and investigator global assessments (1-5) patient pain* OA Severity Index (0-24) (includes pain, walking distance and ADL) WOMAC OA Index APS patient outcome scores; SEM OA severity index; pain measures; GI, renal and other adverse effects	Celecoxib: significant improvement all OMs 50mg/100mg/200mg bd superior to placebo (p<0.05): all OMs except patient assessed pain for 50mg. 50mg less SS effective than 100mg but not 200mg in WOMAC Data suggests higher dose celecoxib onset at 2 days of (p<0.05)
Williams 2000 (44;45) celecoxib 2 x 100mg/day or 2 x 200mg/day placebo N=455, 6 weeks, knee ARC functional class I-III no concomitant therapy paracetamol rescue aspirin permitted if continuous	patient and investigator global assessments (1-5) Steinbrockers functional capacity (1-4) Lequesne OA severity Index patient arthritis pain* WOMAC OA Index, OA severity index; GI and other adverse effects LOE withdrawals	all OMs: both celecoxib doses produced SS equivalent improvements that were superior to placebo LOE approx 25% placebo withdrew cf<10% celecoxib (statistically significant difference)
Geis 1999 (43) celecoxib 2 x 50 or 100 or 200mg/day placebo N=853, 12 weeks, hip 28-93 yoa	patient and investigator global assessments patient pain assessment* OA severity index	Celecoxib (all doses) superior statistically significant reduction in pain at all assessments (p<0.05). no statistically significant differences between celecoxib doses

Celecoxib vs. NSAIDs: osteoarthritis

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
Bensen 1999 (40-42;95) (49) 2 x 500mg/day naproxen celecoxib 50mg/bd or 100mg/bd or 200mg/bd N=800, 12 weeks, knee ARC functional class I-III no concomitant therapy >18 yoa aspirin and paracetamol rescue	patient and investigator global assessments (1-5) patient pain* OA Severity Index (0-24) (includes pain, walking distance and ADL) WOMAC OA Index APS patient outcome scores; SEM OA severity index; pain measures; GI, renal and other adverse effects	Celecoxib: significant improvement all OMs maximum response evident within 2 weeks 100mg/200mg bd equivalent efficacy to naproxen: all measures all time points (p>0.05) except osteoarthritis severity index: 100mg superior to naproxen. Naproxen and higher celecoxib superior to 50mg celecoxib patient pain assessments and WOMAC
Geis 1999 (43) celecoxib 2 x 50 or 100 or 200mg/day naproxen 50mg bd N=843, 12 weeks, hip 28-93 yoa	patient and I Global assessments patient pain assessment* OA severity index	no statistically significant differences between celecoxib (all doses) and naproxen

Celecoxib vs. placebo: rheumatoid arthritis

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
Simon 1998 (39) celecoxib 100 /200mg /day placebo N=249, 4 weeks Steinbroker functional I-III CCX and DMARDs concomitant therapy permitted	investigator and patient global assessments patient pain assessment* joint swelling # joint tenderness/pain duration morning stiffness functional capacity CRP	SS reduction in 400mg/200mg groups difference SS from placebo in patient global assessment (p≤0.001), #tender painful joints(p≤0.005), and ACR criteria (p≤0.025)
Simon 1999 (37;38) celecoxib 2 x 100mg or 2 x 200mg or 2 x 400mg/ day placebo N=924, 12 weeks >18 yoa ARC functional class I-III DMARDs and GCX permitted paracetamol rescue	patient and investigator global assessments (1-5) patient pain* #painful/tender joints #swollen joints duration morning stiffness health assessment q functional disability index CRP ARC-20 improvement	Celecoxib SS improvement from baseline for all measures maximal effects by week 2 sustained through 12 weeks SS greater than placebo

Celecoxib vs. NSAIDs: rheumatoid arthritis

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
Emery 1999 (35;36) celecoxib 2 x 200mg/day diclofenac 2 x 75mg SR N=655, 24 weeks 20-85 yoa ARA <III DMARDs/ CCX permitted SS more patients receiving CCX on diclofenac than celecoxib	patient and investigator global assessments # tender or painful joints # swollen joints patient tenderness (0-3) patient swelling (0-3) #patients responding to ACR-20 responder index functional disability score * duration morning stiffness pain score * (VAS); morning stiffness CRP LOE withdrawals	no SS difference between groups in any OM except #painful/tender joints at week 16 celecoxib superior
Simon, 1999 (37) (38) celecoxib 2 x 100mg or 2 x 200mg or 2 x 400mg/day naproxen 500mg <i>bd</i> N=918, 12 weeks >18 yoa ARC functional class I-III DMARDs and GCX permitted paracetamol rescue	patient and investigator global assessments (1-5) patient pain* #painful/tender joints #swollen joints duration morning stiffness health assessment q functional disability index CRP ARC-20 improvement	celecoxib and naproxen equivalent naproxen not SS greater than placebo both global assessments at week 12. Other OMs show SS greater improvement

Table 3.12 Rofecoxib

Rofecoxib vs. placebo: rheumatoid arthritis

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Schnitzer, 1999 (50) rofecoxib 5 or 25 or 50mg/day placebo N=658, 8 weeks >18 yoa history of therapeutic benefit from NSAIDs and to have used therapeutic NSAIDs for ≥ 25 of last 30dys preceding study entry DMARDs permitted oral CCX or MTX but not both but stratified for MTX no SS differences at baseline paracetamol rescue</p>	<p># patients in each group meeting ACR 20 response \$ # tender joints /68 #swollen joints/66 patient global assessments* investigator global assessment (0-4) patient global pain * CRP</p> <p>QOL: Stanford Health Assessment Questionnaire Disability Index (0-3)</p>	<p>5mg not SS different from placebo 25mg, 50mg #patients with ARC 20 > placebo (p=0.025, 0.001). Also with pt mean change pain, disease activity, investigator global, SHAQ DI (p<0.001). Clear separation between 5mg/placebo and higher dose. rofecoxib similar efficacy in patients taking MTX compared to those not</p> <p>QOL: 25mg, 50mg #patients with SHAQ DI (p<0.001).</p>

\$ 20% improvement in tender and swollen joint counts and 20% improvement in 3 of 5 remaining core measures

Rofecoxib vs. NSAID: rheumatoid arthritis

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p><u>Bombardier, 2000 (12)</u> <u>Confidential</u></p>		

Rofecoxib vs. placebo: osteoarthritis

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Ehrich, 1999 (60)25 or 125mg/day rofecoxib Placebo N=219, 6 week, knee >40 yoa ARA I to III positive NSAID response previous and to be taking NSAIDs prior to entry previous GI excluded paracetamol rescue no data on concomitant</p>	<p>WOMAC pain Patient pain * WOMAC physical function/stiffness investigator and patient global response (0-4) investigator and patient global disease status (0-4) LOE withdrawals</p>	<p>LOE: rofecoxib SS <placebo p<0.001 all endpoints rofecoxib SS superior to placebo (p<0.001). Although some separation in response curves no SS differences between doses (p<0.05). improvement occurring at week 1 (SS WOMAC pain) and SS at week 2 other outcomes</p>
<p>Day 2000 (55;56) rofecoxib 12.5 or 25mg/day placebo N=560, 6 weeks, knee or hip rescue paracetamol stratified into previous NSAID and previous paracetamol >40 yoa ARA Steinbrocker I-III no aspirin or CCX</p>	<p>WOMAC: Pain on walking, pain, stiffness, disability patient global disease* patient overall response(0-4) investigator overall disease status (0-4) investigator overall response joint tenderness (0-3) paracetamol consumption LOE withdrawals</p>	<p>rofecoxib SS reduction all OMs and SS superior to placebo LOE : SS fewer withdrawals in active compared to placebo (p≤ 0.009) maximum effects within 2 weeks</p>
<p>Truitt 1999 (52) rofecoxib 12.5 or 25mg/day placebo N=341, 6 wks, knee or hip ≥80 yoa aspirin permitted</p>	<p>patient global disease status* investigator global disease status (0-4) WOMAC</p>	<p>all OMs rofecoxib SS superior to placebo (p≤0.001)</p>
<p>Ehrich 1997(59) rofecoxib 5 or 12.5 or 25 or 50mg/day Placebo N=672, 6 weeks, knee and hip no inclusion/exclusion details</p>	<p>WOMAC: pain on walking, stiffness, disability patient global assessment response investigator global assessment disease status</p>	<p>all rofecoxib groups SS superior to placebo (p<0.001) all OMs. dose response higher doses superior to 5mg ?SS</p>

Geba 1999(57) rofecoxib 12.5mg/day placebo n=632, 6 wks, knee no inclusion/exclusion details	patient global response (0-4)	rofecoxib SS superior to placebo in number of patients with good or excellent response at 2, 4, and 6 wks (p<0.001)
Saag 1998 (51) rofecoxib 4 x 12.5mg or 25mg placebo n=515, 6 weeks, hip and knee patients with increased pain following NSAID withdrawal and patients with moderate symptoms taking paracetamol	WOMAC: pain on walking*, stiffness, disability patient global assessment response investigator global assessment disease status	all rofecoxib groups SS superior to placebo (p<0.001) all OMs

Rofecoxib vs. NSAIDs: osteoarthritis

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
Cannon 2000 (54;96) rofecoxib 12.5 or 25mg/day diclofenac 3 x 50mg/day N=784, 52 weeks, hip and knee >40 yoa Steinbrocker I-III stratified depending on whether prior NSAID or paracetamol no aspirin or CCX no prior GU or GI bleed rescue paracetamol	WOMAC index: pain when walking*, pain, stiffness, functional ability joint tenderness (0-3) investigator global disease status (0-4) patient global disease status * patient global response to therapy (0-4) investigator global response to therapy(0-4) Rescue paracetamol LOE withdrawals	LOE: no SS difference SS improvement from baseline all groups, all OMs. No SS effect for location of joint i.e. hip or knee, previous medication, age or sex. No SS differences between comparators All primary: treatment response within 2 weeks and maintained throughout study. Although differences between therapies within a priori defined limits, diclofenac SS superior for pt response to therapy and investigator disease status.
Day 2000 (55;56) rofecoxib 12.5 or 25mg/day ibuprofen 3x 800mg/day N=735, 6 weeks, knee or hip stratified into previous NSAID and previous paracetamol >40 yoa ARA Steinbrocker I-III no aspirin or CCX rescue paracetamol	WOMAC: Pain on walking, pain, stiffness, disability patient global disease* patient overall response(0-4) investigator overall disease status (0-4) investigator overall response Joint tenderness (0-3) Paracetamol consumption LOE withdrawals	All responses SS and no SS differences between groups although some separation evident from graphs. Maximum responses within 2 weeks and sustained Rofecoxib 25mg superior to ibuprofen (p=0.005) for pt response and investigator global disease status. Treatment effects consistent for knee v hip, paracetamol v NSAID
Truitt 1999 (52)	Patient global disease status*	Results similar – but no reported results of significance

rofecoxib 12.5 or 25mg/day nabumetone 1500mg /day N=341, 6 weeks, knee or hip ≥80 yoa aspirin permitted	Investigator global disease status (0-4) WOMAC	tests in abstract.
Geba 1999(57) rofecoxib 12.5mg/day nabumetone 1000mg/day N=834, 6 wks, knee no inclusion/exclusion details	patient global response (0-4)	Rofecoxib SS superior to nabumetone in number of patients with good or excellent response at 2,4,and 6 wks (p<0.05)
Saag 1998 (51) rofecoxib 4 x 12.5mg or 25mg ibuprofen 800mg <i>tds</i> N=667, 6 weeks, hip and knee patients with increased pain following NSAID withdrawal and patients with moderate symptoms taking paracetamol	WOMAC: pain on walking*, stiffness, disability patient global assessment response investigator global assessment disease status	No SS differences between groups

Table 3.13 Meloxicam

Meloxicam vs. placebo: osteoarthritis

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
Yocum 1999 (64) meloxicam 7.5mg or 15mg /day placebo N=467, 12 weeks, hip and knee no inclusion/exclusion criteria stated	WOMAC total patient pain patient and investigator global	meloxicam 7.5 mg and 15mg treated patients showed a SS improvement from baseline (p<0.001) which was SS superior (no p value) to placebo in all outcomes.

Meloxicam vs. NSAIDs: osteoarthritis

STUDY	OUTCOME MEASURES	QOL	TOLERABILITY	OTHER
Goei The 1997(68) Knee N=258, 6 weeks 15mg/day meloxicam 100mg/day diclofenac	Pain on movement; Patient global efficacy 100mm VAS 24h worst pain at rest 100mm VAS; Lequesne index of severity; Paracetamol consumption LOE withdrawals Trend in favour of meloxicam in pain, global and paracetamol consumption but not SS	None	Last visit * and global No SS difference	Can calculate ES
Hosie 1996 (66) 7.5mg/day meloxicam 100mg/day diclofenac N=336, 26 weeks Hip and knee	Overall pain 7 days * pain on movement * duration of stiffness global efficacy * paracetamol consumption Improvements in both groups in all parameters but no SS differences	Selected sections of NHP No SS differences	Global tolerance * No SS differences	ES can be calculated
Hawkey, 1998 (70) 7.5mg/day meloxicam 100mg/day diclofenac N=9,323, 4 weeks All OA	Pain on movement* Pain at rest* I and Pt Global efficacy: 4 point scale Pt Change in condition: 3 point scale Pt overall condition: 4 point scale I overall change: 3 point scale	None	Pt and I Global tolerance: 4 point scale Good/satisfactory in 90% meloxicam and 87% diclofenac	Check with RT????

	<p>LOE</p> <p>Diclofenac SS superior all outcomes. 4.5 to 9% difference in ratings. LOE: OR 1.66 (1.16 to 2.38) in favour of diclofenac. Withdrawals due to LOE and/or ADRs p=0.0014 in favour of diclofenac.</p>		(p=0.001)	
<p>Yocum 1999 (64)</p> <p>Meloxicam: 7.5mg or 15mg/day (3.75mg)</p> <p>Diclofenac: 2 x 50mg</p> <p>N=463, 12 week</p> <p>Hip and Knee</p>	<p>WOMAC total.</p> <p>Patient pain</p> <p>Patient and investigator global</p> <p>SS not reported but data suggests diclofenac superior all parameters. Fewer LOE withdrawals 10.5% cf 16.8/15.9%</p>	None	None	Diclofenac increased incidence of GI events and withdrawals no significance tests reported
<p>Hosie, 1997 (67)</p> <p>Meloxicam: 15mg/day</p> <p>Piroxicam: 20mg/day</p> <p>N=455, 26 weeks</p> <p>Hip and Knee</p>	<p>Overall pain*</p> <p>Global efficacy*</p> <p>pain on movement* duration of stiffness</p> <p>LOE withdrawals</p> <p>Concomitant paracetamol</p> <p>No SS difference</p> <p>12 weeks but at 6 months Meloxicam group SS less overall pain but validity of using VAS after 6 months questionable and only approx 50% of patients remained with last values carried forward. Graph shows visit number and not time interval- misleading</p>	<p>NHP</p> <p>No SS difference any subscale; physical mobility, energy level, social isolation and influences.</p>	<p>Overall tolerability*</p> <p>Withdrawals due to poor tolerability</p> <p>#ADRs</p> <p>global tolerability*</p> <p>No SS differences any parameter but Meloxicam lower scores.</p>	
<p>Dequeker, 1998 (71)</p> <p>Meloxicam 7.5mg/day</p> <p>piroxicam 20mg/day</p> <p>N=8,965, 4 weeks</p> <p>all osteoarthritis</p>	<p>Pain on movement*</p> <p>Pain at rest*</p> <p>I and Pt Global efficacy: 4 point scale</p> <p>Pt Change in condition: 3 point scale</p> <p>Pt overall condition: 4 point scale</p> <p>I overall change: 3 point scale</p> <p>LOE</p> <p>No significant differences between comparators in any of parameters measured</p>	None	<p>Pt and I Global tolerance: 4 point scale</p> <p>Good/satisfactory in 90% Meloxicam and 88% piroxicam</p>	

<p>Linden 1996 (65) Meloxicam 15mg/day piroxicam20mg/day N=256, Hip 6 weeks</p>	<p>Worst pain on movement in 24h* Worst pain at rest 24h* global efficacy* LOE withdrawals Paracetamol consumption Lequesne's index of severity</p> <p>Continual pain reduction in pain over trial period. Trend in favour of Meloxicam but no SS difference in primary</p>	<p>None</p>	<p>Pt and I Tolerance* at each visit and global tolerance *</p> <p>No difference in tolerance at any visit. End of study global: Meloxicam approaching SS favourable (p=0.054) in explanatory analysis but not in ITT.</p>	
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related to paracetamol consumption (p<0.003)and baseline pain values(p=0.0001).

Table 3.14 Etodolac

Etodolac vs. NSAIDs: osteoarthritis

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
Perpignano1994 (93) etodolac 600mg/day tenoxicam 20mg/day N= 120, 8 weeks, knee and hip Over 65 years of age history of positive response to anti-inflammatory drugs	global pain* pain on movement (PAM) (1-5) pain at night (1-5) joint tenderness (1-5) joint motility at flexion Lequesne score patient global overall clinical condition investigator global overall clinical condition	SS improvement both groups all parameters with no SS differences between groups etodolac group only: slight but significant improvements in global clinical condition trend suggesting tenoxicam more mobility but more PAM p<0.02
Rogind, 1997 (94) etodolac 2 x 300mg/day piroxicam 20mg/day N=271, 8 weeks, hip and knee Over 40 years of age No concomitant paracetamol rescue	Range of motion (goniometer) Contraction Joint swelling tenderness (1-5) Crepitus (yes/no) investigator overall clinical assessment (1-5) patient: weight bearing pain (1-5) patient: pain at rest (1-5) Duration of joint stiffness (minutes) patient overall clinical assessment (1-5) <i>NB all change in all variables from baseline to end of treatment analysed using 3 point scale improved/no change/worse</i>	both groups SS improvement in all primary at 4 and 8 weeks no SS differences between groups in any variable in both groups for each outcome approx 50% patients experience no change/worse

Etodolac vs. NSAID/aspirin: rheumatoid arthritis

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
Jacob 1985 (78) titrated doses of etodolac between 300-600mg/day titrated levels of aspirin to 4800mg/day N=275, 51 weeks	# painful joints # swollen joints morning stiffness (hrs) grip strength (mmHg)	data questionable: first four weeks not equivalent in terms of therapeutic doses as in titration period. Twice as many patient withdrew due to lack of efficacy in etodolac group during first four weeks but no pt numbers

<p>history of positive therapeutic response functional class/progression stage I to III paracetamol rescue</p>	<p>50 ft walking time (secs) investigator global clinical patient self assessment pain intensity articular index (#painful/swollen joints) ESR;</p>	<p>given for efficacy results. both groups SS improvement all variables (p < 0.05) at all time periods after titration</p>
<p>Lightfoot 1997 (90) etodolac 200mg <i>bd</i> etodolac 300mg <i>bd</i> piroxicam 20mg <i>qid</i> N=426, 12 week 18 to 75 yoa positive response ARA diagnostic criteria no concomitant NSAIDS paracetamol rescue CCX and DMARDS permitted</p>	<p>investigator and patient Global assessments (1-5) # painful joints (/69) # swollen joints(/66) pain intensity (1-5) painful joint score (0-3) swollen joint score(0-3) articular index grip strength (mmHg) ESR duration morning stiffness(min) time to walk 50 ft(sec)</p>	<p>all 3 groups significant improvement in primary at 12 weeks E300 equivalent to piroxicam in all cases E200 significantly less improvement than other groups week 4 patient global</p>
<p>Neustadt 1997 (91) etodolac 300mg/day etodolac 1000mg/day ibuprofen 2400mg/day up to 3 years early stage RA ARA DMARDS not permitted low dose prednisolone <5mg/day permitted</p>	<p>investigator and patient global assessment (1-5) # painful joints # swollen joints ACR remission of RA (duration of morning stiffness, fatigue, joint pain by history, joint tenderness or pain in motion, soft tissue swelling in joints or tendon sheaths, ESR) morning stiffness grip strength time to walk 50 ft articular index time to onset of fatigue joint pain by history Steinbrock's disease stage ACR functional class ESR, RF and CRP</p>	<p>first 2 months: low and high dose etodolac equivalent to ibuprofen with later trend suggesting etodolac superior etodolac SS> ibuprofen #swollen joints from 14 weeks high dose etodolac SS to ibuprofen: patients global Similarly both etodolac doctors global although not SS at all visits neither drug altered disease progression no other SS differences between patient groups subgroup analysis no difference sex, age, type RA onset, family history, duration of RA, #swollen joints, duration morning stiffness</p>

3.3. Effectiveness results: beneficial effects

Celecoxib

Efficacy in rheumatoid arthritis

Both placebo-controlled studies retrieved demonstrated that celecoxib was able to produce a statistically significant reduction against all outcome measures, which was clinically superior to that achieved with placebo (37;39). One of these studies also showed that the maximal effects were evident by 2 weeks, although consideration must also be given to the fact that concomitant use of DMARDs and glucocorticoids were permitted(37). The patients included in a naproxen study arm in one of the studies were shown to have equivalent improvement in disease (37), although the global assessments failed to find any significant difference between naproxen and placebo. The final study compared celecoxib to diclofenac (75mg SR *b.d.*) and the only statistically significant difference found was a superiority of celecoxib in reducing the number of painful/tender joints at week 16 (35;36).

Efficacy in osteoarthritis

Three placebo controlled trials in patients with OA of the knee (40;44) and hip(43). All showed celecoxib to be clinically superior to placebo with no differences between doses of 200 and 400mg/day. Two of the studies also included naproxen 500mg *b.d.* as a comparator (40;43)and the improvement seen in the study groups was shown to be statistically equivalent. Naproxen and higher doses of celecoxib were shown to be superior to celecoxib 50mg *b.d.*.

Rofecoxib

Efficacy in rheumatoid arthritis

Two studies examined efficacy in RA, both of which permitted concomitant therapy with DMARDs and corticosteroids. In an 8 week study involving 658 patients 25mg and 50mg daily produced statistically significant improvements in terms of ACR-20 criteria compared to 5mg and placebo, which were found to be equivalent(50). The external validity of the study results are however limited because all included patients had a history of therapeutic benefit from NSAIDs and were also receiving NSAIDs in at least 25 of the 30 days preceding the trial. The second study found rofecoxib (50mg/day) to be equivalent to naproxen (1g/day) in 8076 patients over 50 years of age treated over a one year period (12).

Efficacy in osteoarthritis

Six 6-week studies, involving a total of 3188 patients, were retrieved that compared rofecoxib, at doses ranging from 12.5mg to 125mg/day, to placebo in

patients with OA of hip and knee(51;52;55;57;59;60). In all cases rofecoxib was found to produce clinically superior benefits to placebo against a variety of outcome measures.

Rofecoxib was compared to other NSAIDs in five RCTs and all comparators were found to produce a statistically significant improvement in disease. There is some suggestion that there may be differences between comparators as two studies found rofecoxib to be superior to ibuprofen (55;56) and nabumetone (57). In each case however, these differences were only evident on the subjective global measures on four-point Likert scales and not on more objective OMs.

Meloxicam

Efficacy in rheumatoid arthritis

Two studies were located which evaluated the efficacy of meloxicam in rheumatoid arthritis. However, neither met the inclusion criteria for this review due to either inadequate duration (3weeks)(62) or because patients could also receive intra-articular corticosteroid injections during the trial period(61).

Efficacy in osteoarthritis

A single 12-week placebo-controlled study was retrieved, which was published in abstract form only, and included 744 patients over 40 years of age with OA of knee or hip(64). Meloxicam treated patients showed a statistically significant improvement from baseline, which was significantly superior to the placebo group against all outcomes measured.

Four studies were located which compared meloxicam to diclofenac (64;66;68;70) and three to piroxicam (65;67;71). In all seven studies, both comparator groups showed a statistically significant improvement from baseline over the trial period, with no statistically significant differences being found between them.

Etodolac

Efficacy in rheumatoid arthritis

Etodolac demonstrated equivalent efficacy to aspirin (78), piroxicam (90) and ibuprofen(91), in producing statistically significant reductions from baseline in all outcome measures, although the validity of the study results are questionable. In the aspirin study the dose was titrated during the first four weeks and in this time period, the report states that twice as many patients withdrew due to lack of efficacy, with no reporting of subsequent patient numbers. Concomitant DMARDs and corticosteroids were permitted in the piroxicam study and low dose prednisolone in the ibuprofen study. No placebo-controlled trials were located.

Efficacy in osteoarthritis

No placebo controlled trials were retrieved. Etodolac (600mg/day) was compared to tenoxicam (20mg/day) (93) and piroxicam (20mg/day) (94) in OA of the hip and knee. In both cases there was a statistically significant improvement in disease as measured by all outcomes with no statistically significant differences between the two comparators. However, the piroxicam study also reported that for each outcome, approximately 50% of patients in each treatment group experienced no change or became worse.

3.4. Effectiveness results: adverse events

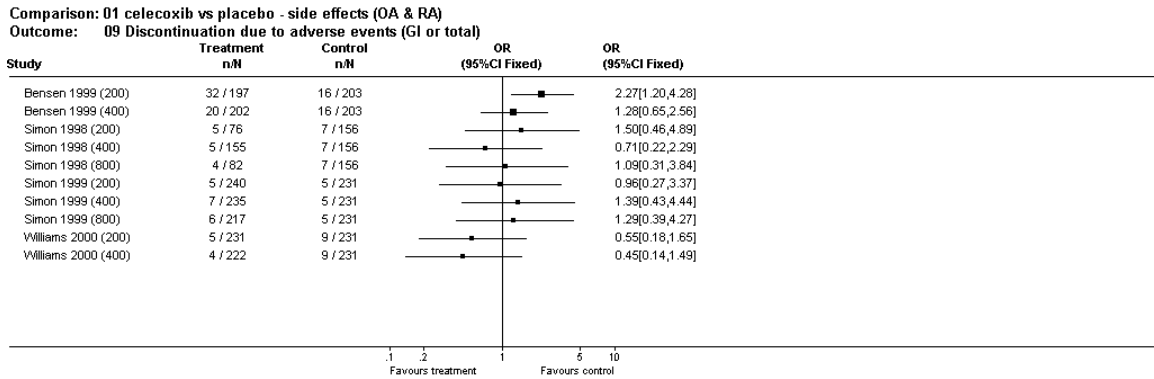
There was considerable variability in the way that the different studies assessed adverse events. Four broad headings of adverse event are therefore presented.

- Total adverse effects: any event not associated with arthritis. The study investigators usually define the severity of event.
- Total gastrointestinal (GI) adverse effects: in most trials this outcome included dyspepsia, abdominal pain, nausea and diarrhoea
- Total withdrawals through adverse effects: withdrawal rate as the result of either GI adverse events or all adverse events
- Perforations, ulcers & bleeding (PUB): assessed clinically or endoscopically

Celecoxib

Of the 13 celecoxib trials selected for review, 8 trials (OA & RA patients) reported adverse outcome data in sufficient detail to allow data to be pooled. A number of the celecoxib trials used more than one dose (i.e. 200mg, 400mg and 800mg daily dose). No consistent trend (either an increase or decrease in event rate) was observed with increasing dosage. An example is shown in the figure below. The event rates across the various celecoxib doses have therefore been summated within each trial.

Figure 1. Comparison of celecoxib dosages (200mg, 400mg and 800mg per day)



Celecoxib versus placebo

Figure 2. Total adverse effects

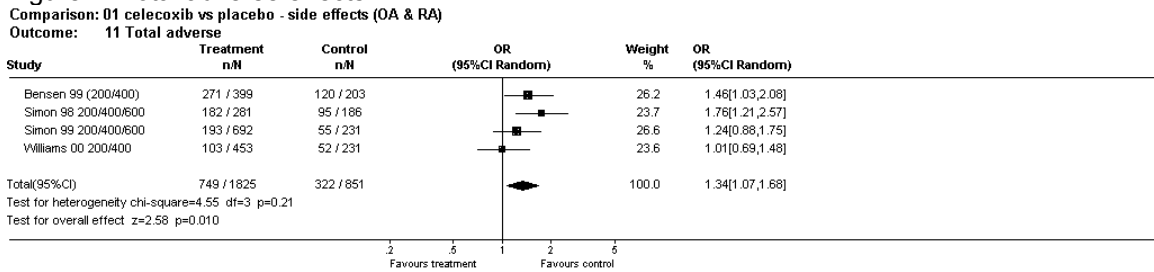


Figure 3. Total gastrointestinal adverse effects

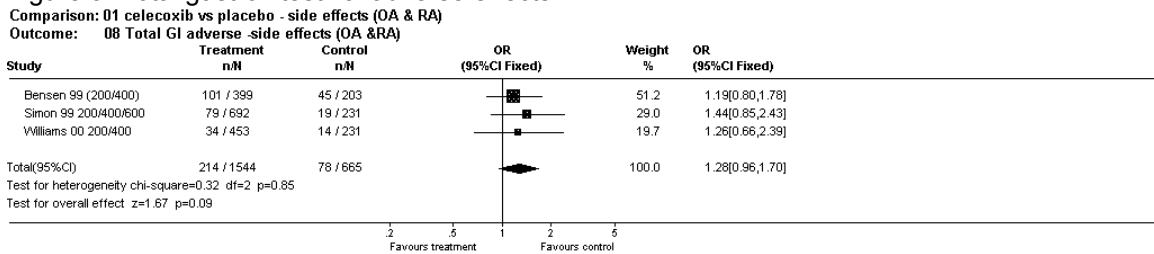


Figure 4. Total withdrawals through adverse effects

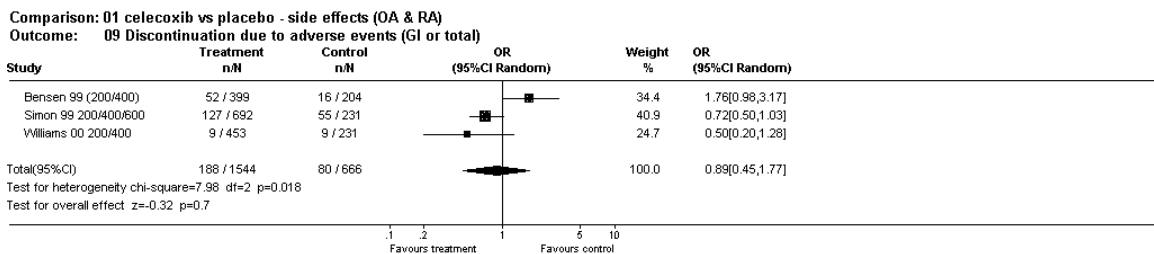
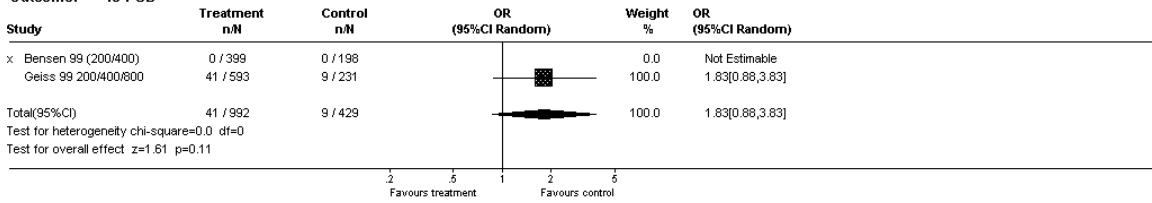


Figure 5. Total PUB

Comparison: 01 celecoxib vs placebo - side effects (OA & RA)
 Outcome: 10 PUB



Celecoxib versus NSAID

Figure 6. Total adverse effects

Comparison: 02 celecoxib vs NSAID -side effects (OA & RA)
 Outcome: 10 Total adverse

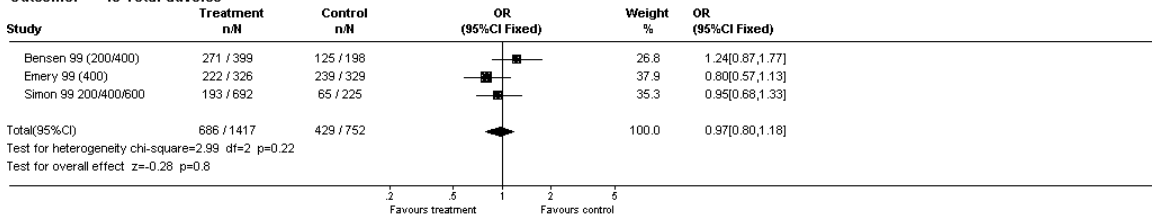


Figure 7. Total gastrointestinal adverse effects

Comparison: 02 celecoxib vs NSAID -side effects (OA & RA)
 Outcome: 07 Total GI adverse

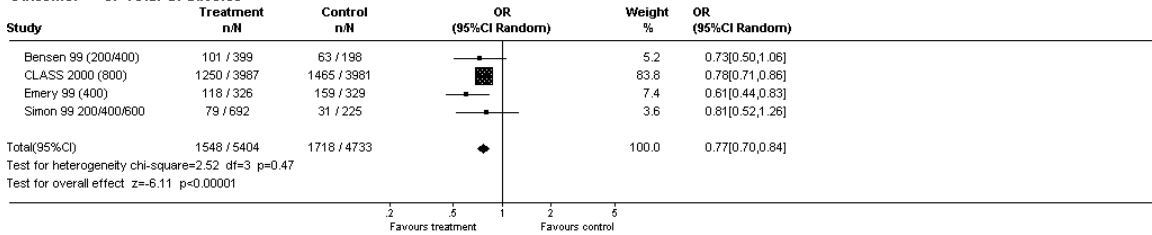


Figure 8. Total withdrawals through adverse effects

Comparison: 02 celecoxib vs NSAID -side effects (OA & RA)
 Outcome: 08 Discontinuation due to adverse events (GI or total)

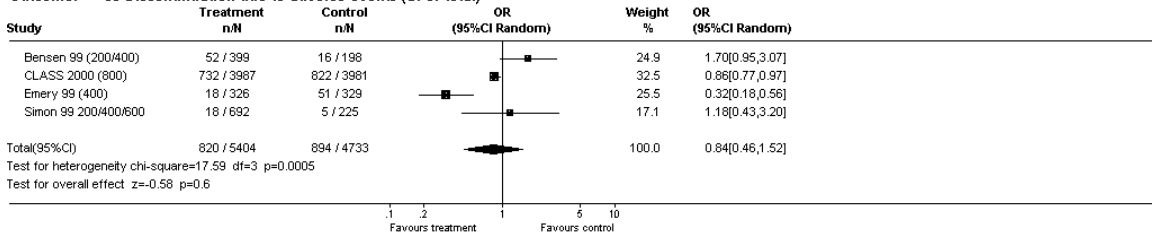
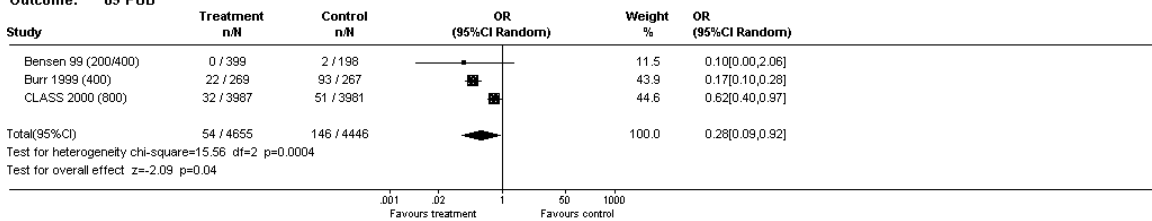


Figure 9. Total PUB

Comparison: 02 celecoxib vs NSAID -side effects (OA & RA)
 Outcome: 09 PUB



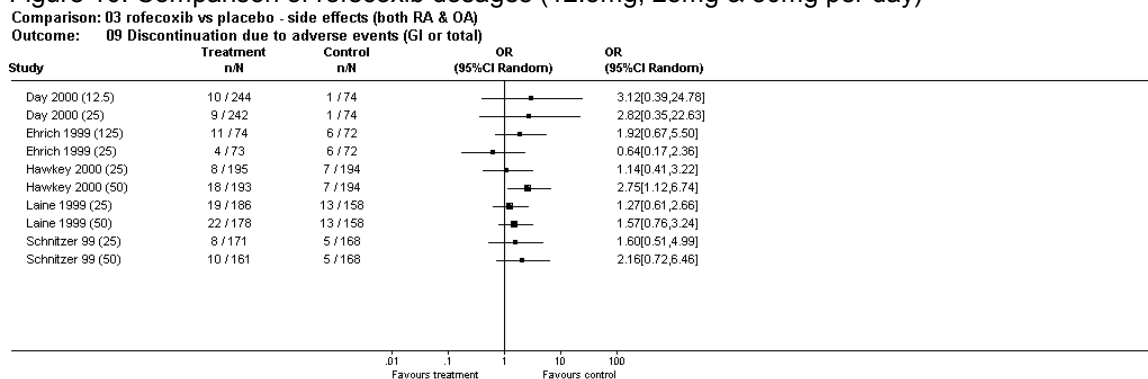
There is evidence from the meta-analysis trials (of 2 to 24 weeks duration) including up to 3,500 OA and RA patients that celecoxib (200 to 800 mg per day), results in a consistent increase in adverse events (both total and GI) and PUB compared to placebo. There appeared to be no difference in withdrawal through adverse rate over that of placebo.

There was considerable heterogeneity in between NSAID trials. Meta-analyses of these trials (which included the comparators naproxen, diclofenac and ibuprofen) including up to 11,000 patients, celecoxib (200 to 800 mg per day) appears to decrease the rate of GI adverse effects, withdrawals and PUB compared to NSAID. No difference in total adverse events was observed.

Rofecoxib

Of the 12 rofecoxib trials selected for review, 7 trials (OA and RA patients) reported adverse outcome data in sufficient detail to allow data to be pooled. A number of the rofecoxib trials used more than one dose (i.e. 12.5mg, 25mg and 50mg daily dose). No consistent trend (either an increase or decrease in event rate) was observed with increasing dosage (see figure 10). The event rates across the various rofecoxib doses have therefore been summated within each trial.

Figure 10. Comparison of rofecoxib dosages (12.5mg, 25mg & 50mg per day)



Rofecoxib versus placebo

Figure 11. Total adverse effects

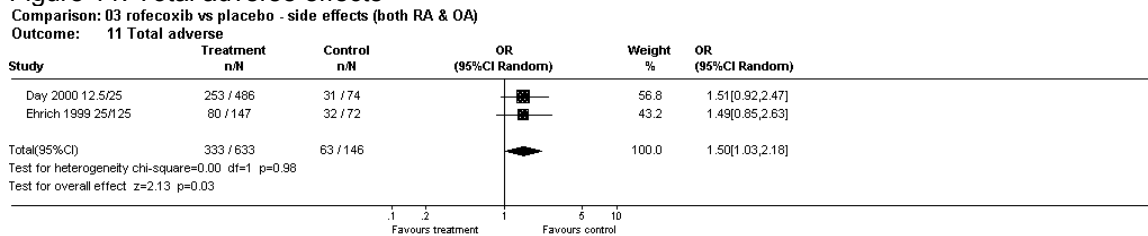


Figure 12. Total withdrawals through adverse effects

Comparison: 03 rofecoxib vs placebo - side effects (both RA & OA)
 Outcome: 09 Discontinuation due to adverse events (GI or total)

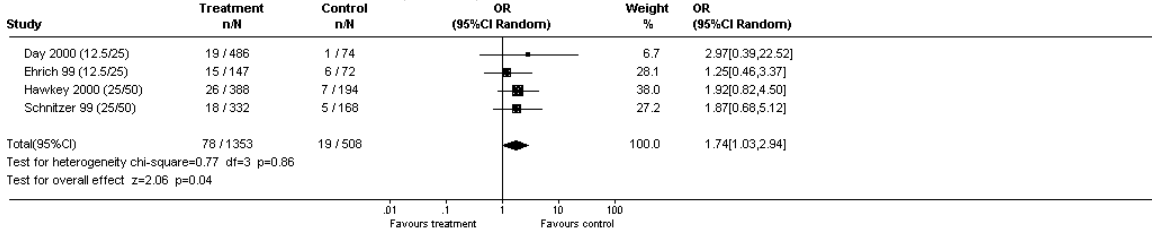
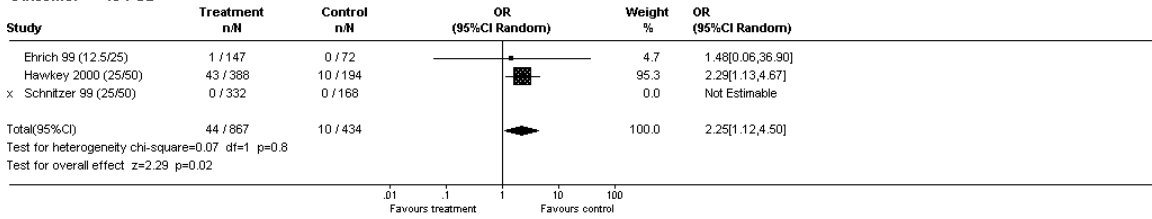


Figure 13. Total PUB

Comparison: 03 rofecoxib vs placebo - side effects (both RA & OA)
 Outcome: 10 PUB



Rofecoxib versus NSAID

Figure 14. Total adverse effects

Comparison: 04 rofecoxib vs NSAID - side effects (both RA & OA)
 Outcome: 11 Total adverse

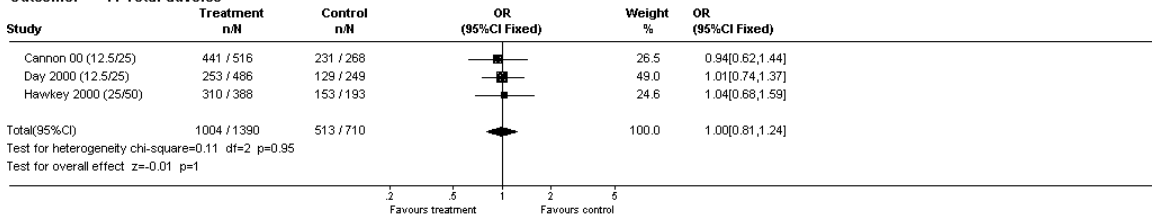


Figure 15. Total withdrawals through adverse effects

Comparison: 04 rofecoxib vs NSAID - side effects (both RA & OA)
 Outcome: 09 Discontinuation due to adverse events (GI or total)

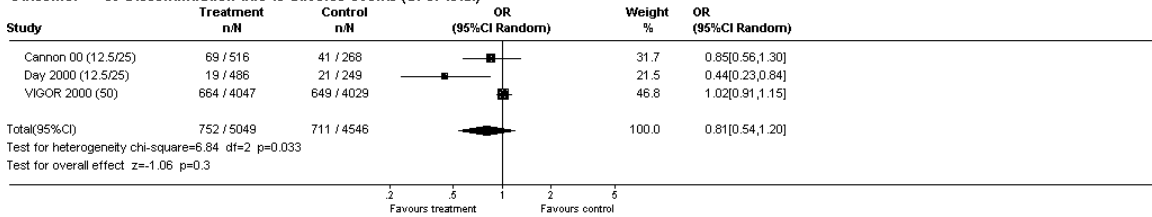
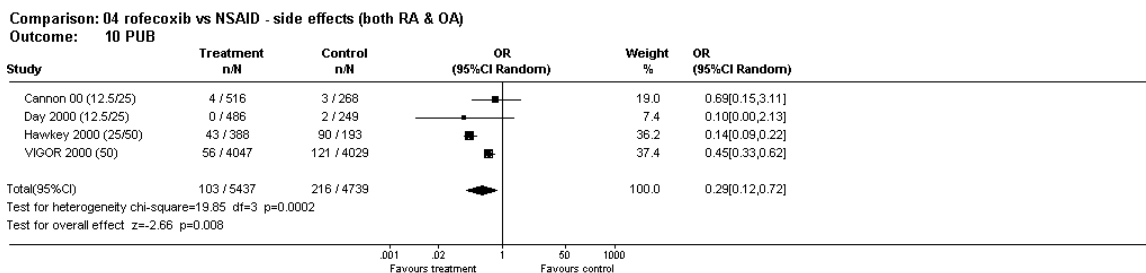


Figure 16. Total PUB

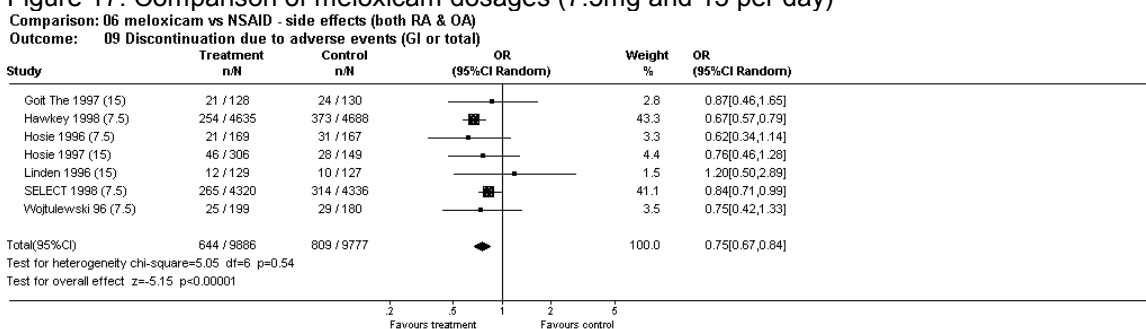


There is evidence from the meta-analysis of placebo-controlled trials including up to 2,200 OA and RA patients of a trend that rofecoxib (12.5 to 50 mg per day) increases total adverse events (GI events not reported separately in the trials), withdrawals due to ADRs and PUBs.. From the meta-analyses of NSAID trials (which included the comparators naproxen, ibuprofen and diclofenac) including up to 10,500 patients, rofecoxib (12.5 to 50 mg per day) appears to decrease PUB compared to NSAID. No difference in total adverse events or rate of withdrawal from adverse events compared to NSAID was observed although GI events were not reported separately.

Meloxicam

Of the 12 meloxicam trials included in the review selected for review, 11 (both OA and RA patients) reported adverse outcome data in sufficient detail to allow data to be pooled. Three studies included a placebo control. . A number of the Meloxicam trials used more than one dose (i.e. 7.5mg and 15mg daily doses). No consistent trend (either an increase or decrease in event rate) was observed with increasing dosage (see figure 17). The event rates across the various doses have therefore been summated within each trial.

Figure 17. Comparison of meloxicam dosages (7.5mg and 15 per day)



Meloxicam versus NSAID

Figure 18. Total adverse effects

Comparison: 06 meloxicam vs NSAID - side effects (both RA & OA)

Outcome: 05 Total adverse

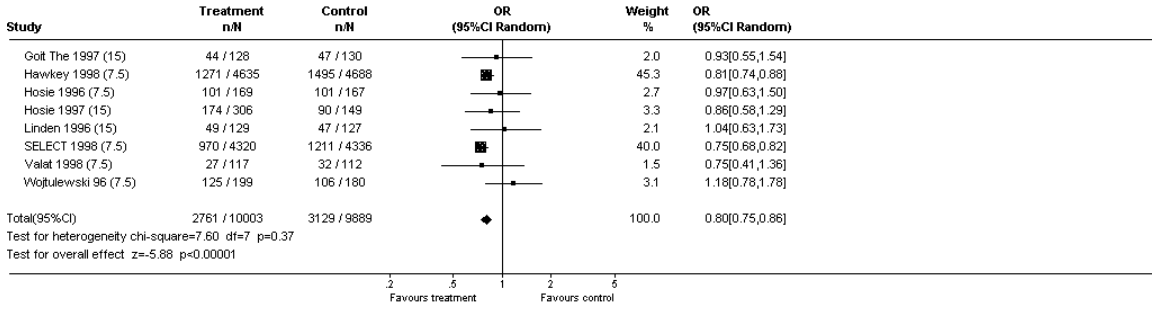


Figure 19. Total gastrointestinal adverse effects

Comparison: 06 meloxicam vs NSAID - side effects (both RA & OA)

Outcome: 12 Total GI adverse

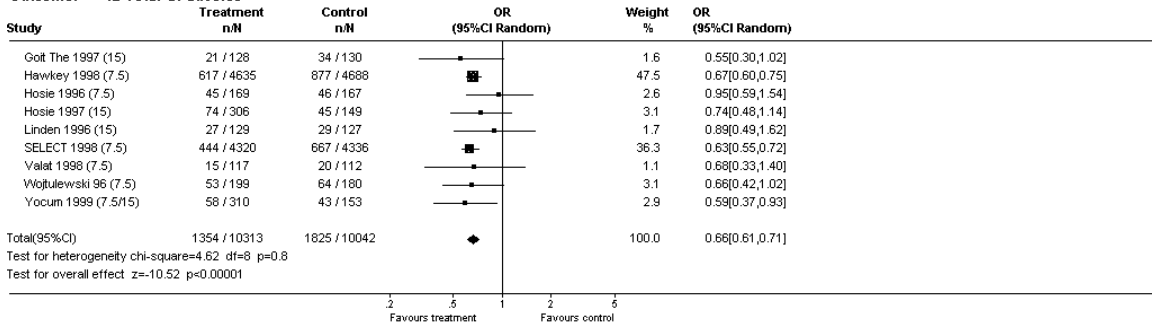


Figure 20. Total withdrawals through adverse effects

Comparison: 06 meloxicam vs NSAID - side effects (both RA & OA)

Outcome: 09 Discontinuation due to adverse events (GI or total)

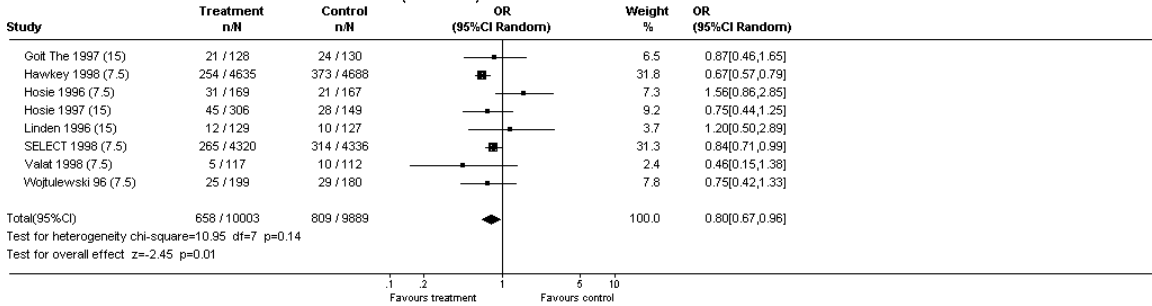
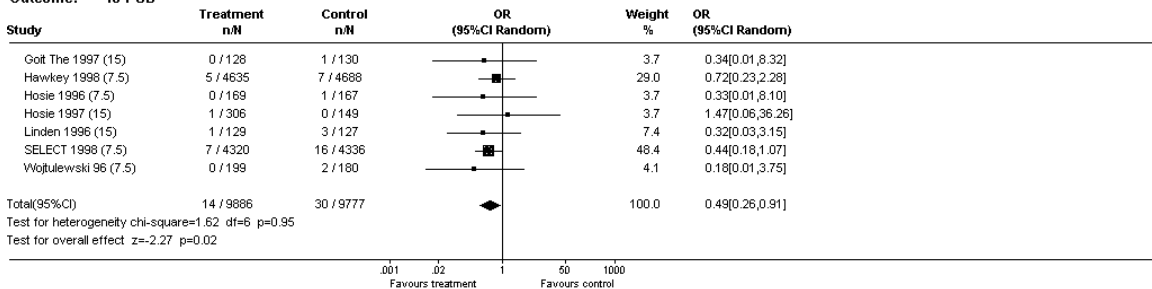


Figure 21. Total PUB

Comparison: 06 meloxicam vs NSAID - side effects (both RA & OA)

Outcome: 10 PUB



Meloxicam vs. placebo

Figure 22: Total adverse effects

Comparison: 05 meloxicam vs placebo - side effects (both RA & OA)

Outcome: 12 Total adverse

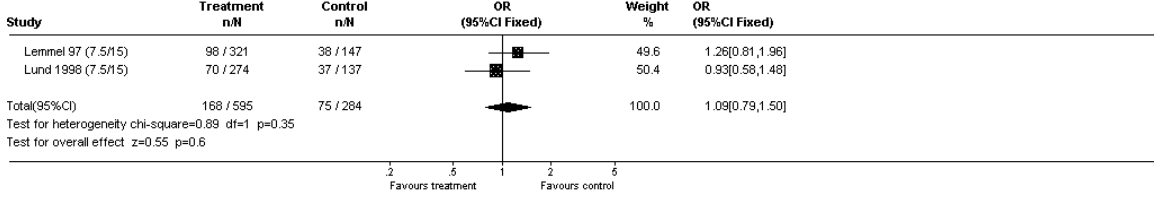


Figure 23: Total Gastrointestinal adverse events

Comparison: 05 meloxicam vs placebo - side effects (both RA & OA)

Outcome: 09 Total GI adverse

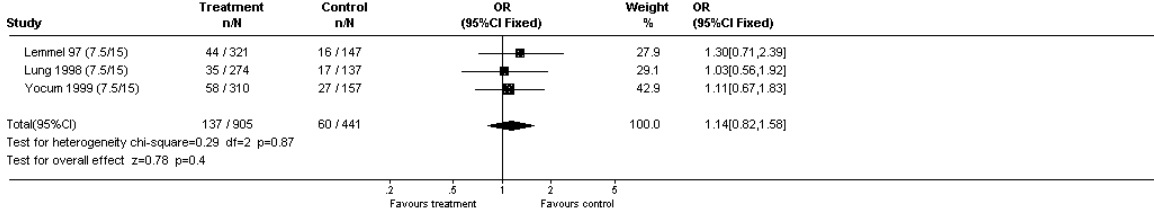
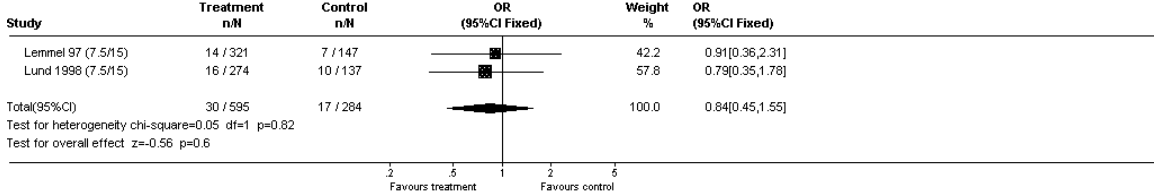


Figure 24: Total withdrawals due to adverse events

Comparison: 05 meloxicam vs placebo - side effects (both RA & OA)

Outcome: 10 Discontinuation due to adverse events (GI or total)



There were three trials identified within this review that compared meloxicam (7.5mg/15mg) to placebo. There was no indication of any difference of meloxicam compared to placebo in terms of total adverse events, GI events or withdrawals. Compared to NSAID (comparators included naproxen, diclofenac and piroxicam) which have included up to 27,500 OA and RA patients, there was evidence of an increase in all adverse outcomes with meloxicam. It appears that the baseline of patients entering the meloxicam trials is lower than those of patients in the celecoxib, etodolac and rofecoxib trials.

Etodolac

Of the 24 etodolac trials selected for review, 7 trials (OA and RA patients) reported adverse outcome data in sufficient detail to allow data to be pooled. Meta-analysis was only performed for trials comparing etodolac to NSAID.

Etodolac versus NSAID

Figure 25. Total adverse effects

Comparison: 08 etodolac vs NSAID - side effects (both RA & OA)
Outcome: 11 Total adverse

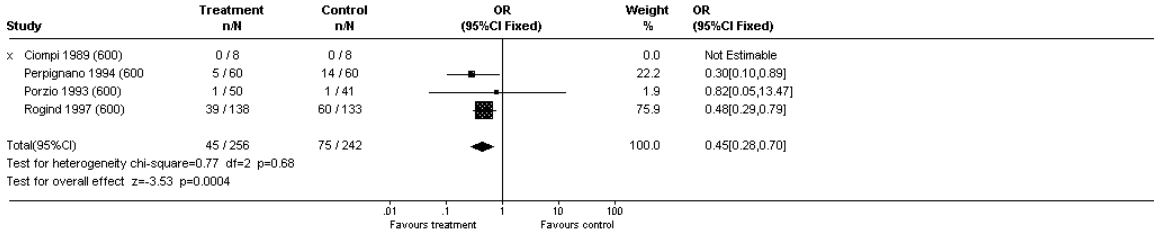


Figure 26. Total gastrointestinal adverse effects

Comparison: 08 etodolac vs NSAID - side effects (both RA & OA)
Outcome: 08 Total GI adverse

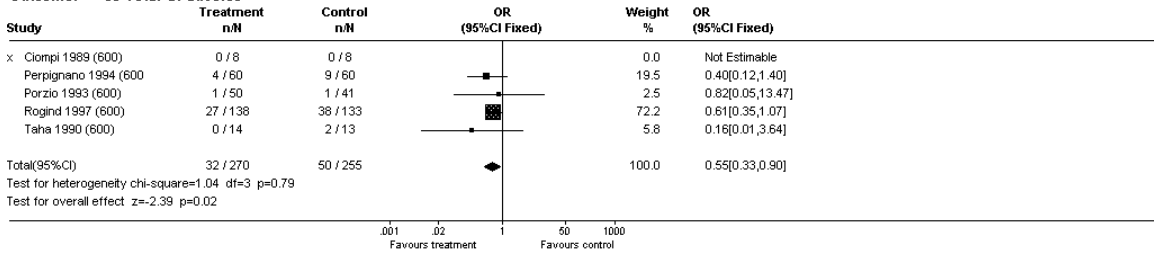


Figure 27. Total withdrawals through adverse effects

Comparison: 08 etodolac vs NSAID - side effects (both RA & OA)
Outcome: 09 Discontinuation due to adverse events (GI or total)

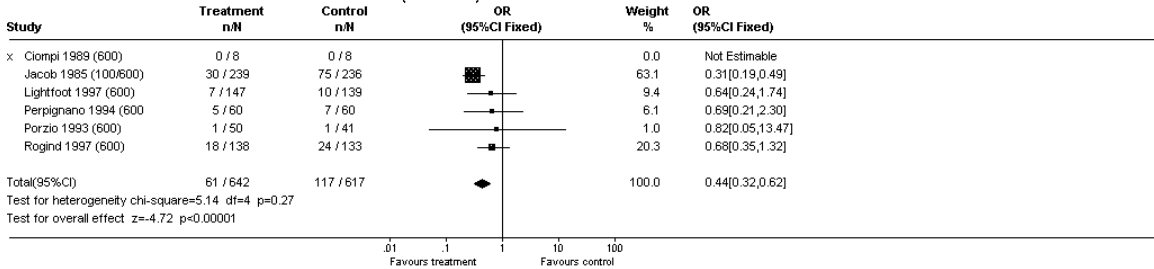
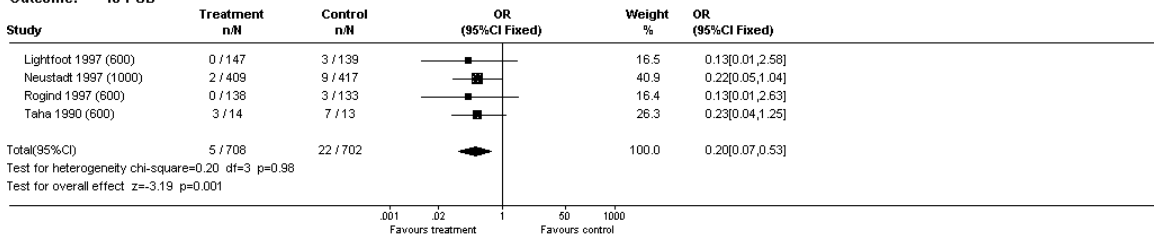


Figure 28. Total PUB

Comparison: 08 etodolac vs NSAID - side effects (both RA & OA)
Outcome: 10 PUB



There were no trials identified that compared etodolac to placebo that reported sufficient information on adverse events to perform a meta-analysis. From meta-analysis trials of etodolac (100 to 1000 mg per day) compared to NSAID (comparators included aspirin, naproxen and diclofenac) based on up to 1800 OA and RA patients, there was evidence of a consistent decrease in adverse events (both total and GI) and PUB compared to NSAID.

Sub group analyses

It is known from the NSAID literature that a number of patient characteristics might influence adverse event rate e.g. advanced age or chronic steroid usage (11). However, sub-group analyses were not reported that addressed this issue. One sub-group analysis was reported that formally addressed the impact of Cox-II inhibitors (versus NSAIDs) on such high risk patients. The industry submission on celecoxib reported ... (in commercial confidence)

4. Economic Evaluation of Cox-II inhibitors

4.1. Results

Literature searches

The literature searches found two economic evaluations related to meloxicam (97;98), and one study comparing coxibs versus other NSAIDs (naproxen, ibuprofen and diclofenac)(99). Two unpublished studies, one comparing celecoxib and naproxen (100) and other comparing celecoxib and rofecoxib with NSAIDs (13) were identified and made available by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA). There are several cost of illness studies for arthritis (25-27), and economic studies for NSAIDs and GPA use (14;101;102), but other than the one identified(99), there are to date no published economic evaluations comparing celecoxib, rofecoxib or etodolac with NSAIDs or with each other. Each of the company submissions contained economic models.

Included studies

The two published economic evaluations identified compared meloxicam to modified release diclofenac, one in the UK and other in a cross-national context (UK, Italy and France). The UK study reported cost savings of £8.96 per OA patient in favour of meloxicam for a 30-day treatment (97), and the latter study reported substantial savings in favour of meloxicam in all three countries when compared with diclofenac; 24% for the UK, 32% for France and 5% for Italy (98).

Motheral et al (99) compared the costs associated with the use of rofecoxib, celecoxib, ibuprofen, naproxen and diclofenac for a three month period in a simple decision analytic model based on local U.S. prices, and reported cost-savings of \$5 (£3.50) for rofecoxib and \$33 (£22) for celecoxib compared with diclofenac for 3 months per patient.

Maetzel & Bombardier have evaluated the cost-effectiveness of (in confidence)

More recently, Maetzel et al carried out a comprehensive economic evaluation comparing..... (in confidence). This study was commissioned by CCOHTA and made available to NICE in draft form (13). The rest of this section will focus on the unpublished work submitted to the Institute from the four manufacturers (31) and also draft CCOHTA report(30;32;33).

Merck Sharp & Dohme submission (Rofecoxib)

The economic evaluation carried out by MSD is based on a decision-tree analysis. This model assumes that all drugs included in the study are equally efficacious and concentrates on GI adverse events that potentially lead to health care resource use. The cost of switching all OA patients currently treated with other NSAIDs to rofecoxib was estimated over a one-year time horizon. The perspective adopted was that of the NHS. The model did not separate meloxicam and etodolac from the other NSAIDs and assumed that they have the same GI safety profiles as all other NSAIDs.

Three different analyses were conducted based on different endpoints and assumptions. Clinically observed PUBs were chosen as an endpoint for GI events in the first analysis, whereas the other two scenarios were based on ulcers ≥ 3 mm detected by endoscopies, in randomised controlled trials, but with different silent ulcer rates. In the second analysis, only 15% of all ulcers were assumed to require treatment (the remaining 85% being “silent”), whereas in the third scenario, the silent ulcer rate was chosen as 40%.

Costs associated with each health state were estimated using a “bottom-up” approach, and validated by comparing the unit costs obtained from three large acute Trusts from three different regions. The costs of conventional NSAIDs were chosen as the average daily cost within the whole class, weighted by market shares¹¹.

Misoprostol and proton pump inhibitors were assumed equally efficacious in prophylactic gastroprotection and to reduce the risk of major GI events by 40%. Rofecoxib was assumed to reduce the gastroprotective agent (GPA) prescriptions by 75%. This assumption was based on an expert panel decision and tested via sensitivity analyses. The results of this economical evaluation are given in Table 4.1. In the first scenario, the cost per PUB avoided and cost per life year saved were estimated to be £10,759 and £15,647 respectively. Cost savings were reported in the other two scenarios.

The iatrogenic cost factors¹² for conventional NSAIDs were 1.97, 3.75 and 8.41 respectively for each scenario, meaning that for each £1 spent on NSAIDs, an additional £0.97 to £7.41 is spent to prevent or treat GI consequences. However, these values, especially those obtained in scenario II and III (3.75, 8.41) seem rather high, when compared with those reported elsewhere in the literature, ranging 1.35-2.53 (103),(101),(104). Iatrogenic cost factors for rofecoxib were estimated to be around 1.15, 1.30 and 1.71 respectively in this model.

¹¹ Market shares were obtained from MediPlus database

¹² The iatrogenic cost factor is the ratio of the total costs incurred by the use of the drug (shadow costs), including the treatment costs for the adverse events, to the drug cost alone.

Table 4.1 Cost effectiveness values for rofecoxib, reported in the MSD submission

	Analysis 1	Analysis 2	Analysis 3
GI event endpoint	Clinically observed PUBs	Endoscopically diagnosed ulcers (85% silent ulcer rate)	Endoscopically diagnosed ulcers (40% silent ulcer rate)
Cost to NHS ¹³ (per patient p.a.)	£ 46.40	-£14.50 (saving)	-£168.20 (saving)
Cost per life year saved	£10,759	Saving	Saving
Cost per PUB avoided	£15,647	Saving	Saving
Cost per life saved	£298,859		

Pfizer & Searle joint submission (Celecoxib)

The joint submission by Pfizer & Searle included a decision analytic model to compare the costs, effects and cost-effectiveness over six months of treatment with celecoxib, NSAIDs alone, NSAIDs combined with GPAs (PPIs, H₂RAs and misoprostol and Arthrotec (diclofenac + misoprostol) in OA and RA patients. Etodolac, meloxicam or rofecoxib were not separately included in the analysis as comparators. Reported incremental cost effectiveness ratios (ICERs) were based on ibuprofen as the main comparator. This model adopted the NHS perspective and did not consider indirect costs. Costs and outcomes were not discounted, with the exception of “cost per LYG” calculations discounted at an annual rate of 2%. The average duration of NSAID treatment was assumed to be 180 days/year.

Data were obtained from company-sponsored celecoxib clinical trials, the literature, a survey of UK clinical practice and several UK databases (including IMS and MEMO).

This model enables patients to switch therapy in case of lack of efficacy and intolerance, and therefore compares alternative management strategies. An algorithm for therapy switching was defined, which they believe reflects the current UK practice.

Patient populations were stratified into different risk groups for GI events by using a simple point scoring algorithm that produces a risk score between 0 (lowest risk) to 44 (highest risk) for each patient, derived from following risk factors; age, history of serious GI events, current use of oral corticosteroids and disability (using HAQ scale). The calculator predicted that the probability of presenting

¹³ Average patient is assumed to have 145 days of NSAID therapy in a year

with a serious GI event is 0.25% for a patient scoring 6 points on the scale. Each additional risk point above that score is assumed to increase the probability of severe GI events per year by 0.25%. Also, a Weibull model was developed to identify the association between GI discomfort rate and potential risk factors. Aspirin use, gender and history of GI events were found to be associated with GI discomfort.

Naproxen was chosen as a comparator when predicting the event rates. The rates were then extrapolated to other NSAIDs according to the relative toxicity values reported in the literature. However, in cost-effectiveness evaluations, generic ibuprofen was chosen as the comparator.

The ICER for celecoxib relative to generic ibuprofen is estimated to be £6,842 per life year gained or £749 per GI event averted. Results are shown in Table 4.7 and based on the average across the population risk group, with a risk score of 12.92. Sensitivity analyses have shown that celecoxib would become cost-saving for people with 35 risk points and above, whereas cost per LYG sharply increases below 13 risk scores (£10,000 at 9 points, £20,000 at 7 points and £40,000 at 6 points). The original submission did not report results for the RA group, cost per PUB for OA or cost per death for OA. We therefore estimated these figures using the data provided by the manufacturer.

Boehringer Ingelheim submission (Meloxicam)

The economic evaluation carried out by Boehringer Ingelheim is based on a cost-minimisation decision-tree analysis, comparing meloxicam (7.5 mg once daily) versus diclofenac retard (100 mg once daily), piroxicam (20 mg once daily) and rofecoxib (12.5 and 25 mg once daily), for the treatment of OA. Celecoxib and etodolac were not included in this study due to lack of comparative evidence. The economic model comparing meloxicam versus diclofenac and piroxicam was constructed over a four-week period, based on the MELISSA and SELECT trials. As there are no “head to head” trials, the meloxicam versus rofecoxib model was constructed upon data obtained from the FDA’s medical advisors report for rofecoxib (rofecoxib versus diclofenac), pooled over 6 months. Both models assume that all drugs included in the study are equally efficacious. The perspective adopted was that of the NHS and only direct costs were covered. Co-prescription of GPAs has not been taken into consideration in these models, due to the unavailability of data.

Information on resource utilisation and costs were obtained mainly from Tayside Medicines Monitoring Unit (MEMO) and the medical literature. Costs were not discounted.

The results of the economic evaluations based on the two different models showed that meloxicam was the most cost-effective option compared with all other NSAIDs included in the study. Meloxicam produced cost savings of £5 and

£21 per patient treated in 4 week trial period (£65 and £273 per patient per annum) when compared with piroxicam and diclofenac. It also demonstrated cost advantages (£40 savings per patient per annum) versus rofecoxib (Table 4.2)

Table 4.2 Results reported in Boehringer Ingelheim submission

	Meloxicam versus		
	Diclofenac	Piroxicam	Rofecoxib
Time frame	4 weeks	4 weeks	6 months
Cost to NHS (per patient p.a.) ¹⁴	-£273 (saving)	-£65 (saving)	-£40 (saving)

Shire submission (Etodolac)

The economic analysis submitted by Shire draws upon an editorial published in JAMA in 1999 by Peterson and Cryer(105). This is based on the assumption that all NSAIDs have comparable efficacy, and incremental cost per PUB avoided was calculated using relative risk reduction ratios and incremental cost of each product, rofecoxib, celecoxib and etodolac. Relative risk reduction for etodolac was chosen to be the same with rofecoxib and celecoxib (0.5) on the assumption that the Cox-II selectivity is at least equal to that of rofecoxib. This analysis only considers drug costs and does not incorporate other direct medical costs, such as hospitalisation or consultations.

The incremental cost to avoid a serious PUB was estimated for low-risk and high-risk patients. High-risk patients were defined as those aged more than 75, those with a history of peptic ulcer or gastric bleeding or a history of cardiovascular disease. The incremental costs to avoid a serious PUB were estimated based on both naproxen and ibuprofen as comparators. In low-risk patients, the incremental cost (per GI event avoided) was estimated as £100,375 to £211,700 for celecoxib, £129,575 for rofecoxib and £83,950 for etodolac, when compared with ibuprofen. For high-risk patients, these costs were calculated to be £7,629 to £16,089 for celecoxib, £9,848 for rofecoxib and £6,380 for etodolac. Considerably lower cost cost-effectiveness values were reported when the comparator was naproxen instead of ibuprofen (Table 4.3)

The authors concluded that the cost-effectiveness of selective Cox-II inhibitors (including etodolac) for use in all patient groups, remains unproven, however cost- effectiveness, in terms of cost per event prevented, appears to be reasonable for high-risk patients.

¹⁴ Assumes 52 weeks of treatment

Table 4.3 Incremental cost effectiveness of selected Cox-II inhibitors (Shire submission)

Cox-II inhibitor	RR ¹⁵	NNT ¹⁶	Incremental cost (£) per person p.a.		Total cost per event avoided (£)	
			Low ¹⁷ -cost	High-cost	Low-cost	High-cost
Low risk patients						
Rofecoxib 12.5 mg/day	0.5	500	135.05	259.15	67,525	129,575
Rofecoxib 25 mg/day	0.5	500	135.05	259.15	67,525	129,575
Celecoxib 200 mg/day	0.5	500	76.65	200.75	38,325	100,375
Celecoxib 400 mg/day	0.5	500	299.30	423.40	149,650	211,700
Etodolac 600 mg/day	0.5	500	43.80	167.90	21,900	83,950
High risk patients						
Rofecoxib 12.5 mg/day	0.5	38	135.05	259.15	5,132	9,848
Rofecoxib 25 mg/day	0.5	38	135.05	259.15	5,132	9,848
Celecoxib 200 mg/day	0.5	38	76.65	200.75	2,913	7,629
Celecoxib 400 mg/day	0.5	38	299.30	423.40	11,373	16,089
Etodolac 600 mg/day	0.5	38	43.80	167.90	1,664	6,380

CCOHTA Study

(in confidence)

Analysis of the economic evaluations

Generally, most of the economic evaluations submitted by industry were structurally well-designed models. The appraisal of these studies using the Drummond checklist is given in Table 4.6. However there were considerable variations in results reported by the different models. These are mainly due to the probabilities attached to different health states and also cost variations. These variations will be explored in detail in the following section.

¹⁵ Relative risk

¹⁶ Number needed to treat

¹⁷ Low cost scenario compares Cox-II inhibitors with naproxen whereas high cost scenario is based on ibuprofen as a comparator.

Table 4.6 Appraisal of the economic evaluations (using the Drummond checklist(106))

	<i>Merck Sharp & Dohme (Rofecoxib)</i>	<i>Pfizer & Searle (Celecoxib)</i>	<i>Boehringer Ingelheim (Meloxicam)</i>	<i>Shire (Etodolac)</i>	<u>CCOHTA Study</u>
<i>Well defined question posed?</i>	Yes	Yes	Yes	Yes	
<i>Description of competing alternatives?</i>	Yes - (but did not consider etodolac, meloxicam and celecoxib separately)	Yes - (but did not consider etodolac, meloxicam and rofecoxib separately)	Yes - (but did not consider etodolac, and celecoxib separately). Concomitant GPA use has not been addressed	Yes - (but did not consider meloxicam separately)	
<i>Effectiveness established?</i>	Yes - (assumed equal efficacy)	Yes - (assumed equal efficacy)	Yes - (assumed equal efficacy)	Yes - (assumed equal efficacy)	
<i>Important costs/ consequences identified?</i>	Yes - only GI adverse effects are considered	Yes - only GI adverse effects and anaemia are considered	Yes-considered all adverse effects	? Only drug costs were included. Ignores other direct costs (e.g. hospitalisation) to the health services.	
<i>Costs/consequences measured accurately?</i>	Yes	Yes	Yes	Yes? Only NNT considered	
<i>Costs/consequences valued credibly?</i>	Yes	Yes	Yes	Yes	
<i>Adjustment for differential timing?</i>	NA-all costs within one year (LYGs were not discounted either)	NA- six months time horizon (discounting only applied to "cost per LYG" calculations at 2%)	NA-less than one year horizon	NA-all costs within one year	
<i>Incremental analysis?</i>	Yes	Yes	Yes	Yes? Incremental cost per event has been estimated	
<i>Uncertainty?</i>	Yes	Yes	Yes	No? Reports incremental cost values for high and low risk groups	
<i>Discussion</i>	Yes	Yes	Yes	Yes	

Table 4.7 Incremental cost effectiveness values of Cox-II inhibitors compared with conventional NSAIDs, reported in the different economic analyses.

	Rofecoxib	Celecoxib ¹⁸	Meloxicam	Etodolac	<u>CCOHTA</u>
Cost per PUB avoided	Sc1 ¹⁹ : £10,759 Sc2: saving Sc3: saving	(any GI event) £749 (OA), £1,145 (RA) (per PUB) ²⁰ ~£3,500 (OA) ~£6,350 (RA)	n.a.	low risk £21,900-£211,700 high risk £1,664-£16,089	
Cost per LYG	Sc1: £15,647 Sc2: saving Sc3: saving	£6,842 (OA) £10,374 (RA) ²¹	n.a.	-	
Cost per QALY			n.a.		
Cost per death saved	Sc1: £298,859	~£120,000 (OA) ~£210,000 (RA)	n.a.		

¹⁸ “Cost per PUB avoided” and “cost per death” values were calculated by the NICE Appraisals Team, using the data submitted by Pfizer & Searle.

¹⁹ Sc=scenario (see section 4.1.2 MSD submission)

²⁰ The number of patients with PUB was calculated by summing the numbers with gastric ulcer and severe GI events, but not with anaemia

²¹ rofecoxib compared with generic ibuprofen

Variations in Event Rates

Some of the differences in the results of the different economic evaluations can be explained by different GI event rates used in each analysis. These probability estimates are given in Table 4.8. Some of these probabilities were not directly comparable in the way they were reported. Therefore we calculated some probabilities directly from the decision trees.

In the CCOHTA report, GI discomfort rates (in confidence)

The MSD and Pfizer & Searle submissions utilise probability estimates calculated by the pooled analysis of company-sponsored clinical trials. The Boehringer Ingelheim submission includes two analyses. The first compared meloxicam with piroxicam and diclofenac within a time frame of 4 weeks, based on the data pooled from MELISSA and SELECT trials (n~9,000 each) (70;71). The second one compared meloxicam versus rofecoxib where the data for the meloxicam arm came from two trials with a total of 475 patients and the rofecoxib data from an FDA submission (n=2,812). There are considerable differences between the probabilities used in each model, i.e. the probability of having an adverse event severe enough to seek GP consultation was 11.7% in the 4-week model and 57.9% in the 6-month model. Therefore each model is reported separately in Table 4.8.

Table 4.8 Event probabilities in each economic evaluation

		Rofecoxib	Celecoxib	Meloxicam		CCOHTA
				4 wks	6 mths	
			6 months			
Any GI event	Generic NSAID	29.46%	15.37%	15.38% (PR ²²) 18.71% (DF-R) ²³		
	Celecoxib		22.88%			
	Rofecoxib	29.87%			18.6%	
	Meloxicam			11.8%	57.9%	
	Etodolac					
Ulcer	Generic NSAID	2.68% (28.47% for endoscopic)	1.92%	0.37% (PR) 0.13% (DF-R)		
	Celecoxib		0.59%			
	Rofecoxib	1.50% (6.33% for endoscopic)			0.2%	
	Meloxicam			0.13%	0.4%	
	Etodolac					
Serious GI events requiring hospitalisation	Generic NSAID	1.09%	0.77%	0.16% (PR) 0.21% (DF-R)		
	Celecoxib		0.33%			
	Rofecoxib	0.52%			>0.1%	
	Meloxicam			0.10%	>0.4%	
	Etodolac					
Death	Generic NSAID	0.096%*	0.11%			
	Celecoxib		0.05%			
	Rofecoxib	0.054%*				
	Meloxicam					
	Etodolac					

*Based on symptomatic ulcers (scenario 1).

²² PR : Piroxicam

²³ DF-R: Diclofenac retard

Variation in Cost Estimates

The variations of cost effectiveness estimates reported in the different submissions are partly due to differences in cost estimates which may be a result of underlying assumptions in resource use and also the way the models are constructed. As seen in Table 4.9, there is considerable variation in unit costs utilised by each model to estimate the health care costs in the management of different GI adverse events. For example, the Boehringer Ingelheim model assumes that a patient with GI events leading to perforation that needs surgery would stay in an intensive care unit for 7.75 days (costing £7,052), while the same patient would cost only £1,000 in MSD model, staying only one day in intensive care.

Table 4.9 Health care utilisation costs in each economic evaluation

UNIT COSTS (per GI event)				
	<u>MSD</u> (rofecoxib)	Pfizer&Searle (celecoxib)	BI (meloxicam)	<u>CCOHTA</u> study
Surgery for PUB	<u>£3,838</u>	–	<i>If ICU</i> £1,636-9,676 <i>No ICU</i> £1,636-3,264	
Inpatients treatment for PUB	<u>£1,715</u>	£2,668 ²⁴ (no hosp.) £3,729 (hosp)	<i>If ICU</i> £1,636-9,621 <i>No ICU</i> £1,636-2,569	
Outpatient treatment for PUB	<u>£675</u>	£393 (ulcer) (£189 for <i>GI discomfort</i>)	£284	
<i>Minor GI problem (requiring no further investigation)</i>	<u>£39</u>	–	£60	

The average daily costs of each drug are given in Table 4.10.. The variations in drug costs are probably due to different dosages and packaging, but may be up to three-fold for some drugs (e.g. ibuprofen). Average duration of NSAID treatment (per year) also differs in each submission. The MSD submission assumed that, on average, the base-case would be on NSAID for 145 days a year, whereas this figure was 180 days in Pfizer & Searle submission.

²⁴ Severe GI event with no hospitalisation

Table 4.10 Drug costs from each economic evaluation

DRUG COSTS (per day)					
	MSD (rofecoxib)	Pfizer&Searle (celecoxib)	BI (meloxicam)	Shire (etodolac)	CCOHTA study
<i>Rofecoxib</i>	0.79		0.77	0.77	
<i>Celecoxib</i>		0.61		0.61-1.22	
<i>Meloxicam</i>	0.38		0.33		
<i>Etodolac</i>	0.55			0.52	
<i>Other NSAIDs²⁵</i>					
<i>Ibuprofen</i>	0.14	0.22		0.06	
<i>Naproxen</i>	0.25	0.26		0.40	
<i>Piroxicam</i>	0.15	0.19	0.14		
<i>Diclofenac</i>	0.29	0.26	0.33		
<i>NSAID (as a whole)</i>	0.30	0.2 ²⁶			
<i>GPA</i> s					
PPI	0.93	1.13			
<i>H₂RA</i>	0.54	0.54			
<i>Misoprostol</i>	0.63	0.36			
<i>Arthrotec®</i>	0.52	0.49			

Differences in the estimated rates for co-prescribing of GPAs are another source of variation in cost calculations. For example, MSD assumed that 20.1% of patients who are on conventional NSAIDs will also be prescribed GPAs, which would be expected to decrease by 75% in rofecoxib group. The CCOHTA report used a GPA co-prescription rate of(in confidence), whereas Boehringer Ingelheim ignored GPAs in their model.

Estimate of Budgetary Impact

Table 4.11 shows the different estimates for potential budgetary impact on the NHS if Cox-II inhibitors are recommended for wider use. Most estimates suggest significant cost savings for the NHS, mainly due to the savings on health care costs of avoided GI events.

MSD estimate that switching from conventional NSAIDs to rofecoxib in all OA patients would cost the NHS an extra £39.5 million per year in scenario 1, which is based on symptomatic ulcers. However in the case of the other two scenarios, they estimated significant cost-savings up to £143m per annum depending on the silent ulcer rates (85% in scenario 2 and 40% in scenario 3, see section 4.1.2 MSD submission).

²⁵ Generic prices unless specified

²⁶ Includes only generic NSAIDs

Pfizer & Searle have followed a slightly different method to evaluate the wider NHS implications in four different scenarios:

- Scenario 1: The objective is to minimise total NHS expenditure on NSAIDs irrespective of the outcomes. All patients were given ibuprofen as a first-line NSAID therapy after simple analgesia.
- Scenario 2: The objective is to maximise health gain, with the cost per LYG threshold of £10,000. 63% of patients receive celecoxib as a first-line therapy and the remainders receive ibuprofen.
- Scenario 3: The objective is to maximise health gain within current budget constraints for OA. 80% of patients receive celecoxib and remainders receive ibuprofen as a first-line therapy.
- Scenario 4: The objective is to minimise GI events irrespective of cost implications. All patients receive celecoxib after simple analgesia.

The anticipated cost impact for each scenario is given in Table 4.11. It is estimated that switching from conventional NSAIDs to celecoxib in all OA patients would cost the NHS an extra £25 million per year (Scenario 4). It should be noted that in this analysis, the estimated number of OA patients who are on NSAID treatment is almost twice the figures used in MSD and Shire submissions, which are both below 1m patients per annum.

Boehringer Ingelheim estimate that cost savings of over £25m may be expected if meloxicam replaces all piroxicam and diclofenac prescriptions in OA patients, based on market shares of each product.

Table 4.11 Estimates of budgetary impact for each Cox-II inhibitor drug

	MSD (rofecoxib)	Pfizer&Searle (celecoxib)	BI (meloxicam)	Shire (etodolac)
<i>Number of patients with arthritis</i>		3,854,970		3,100,000
<i>Eligible patients for NSAID use</i>	848,722 (OA)	1,870,730		930,000
<i>Incremental cost per patient per annum</i>	Sc 1: £ 46.4 Sc 2: -£14.5 (saving) Sc 3: -£168.2 (saving)		Cw diclofenac:-£273 (saving) Cw piroxicam:-£65 (saving) Cw rofecoxib: -£40 (saving)	Not reported
<i>Total additional annual cost to NHS</i>	Sc 1 ²⁷ : £39.5m Sc 2: - £12m (saving) Sc 3: - £143m (saving)	Sc 1 ²⁸ :-£62m (saving) Sc 2:-16m (saving) Sc 3: cost-neutral Sc 4: £20m	Saving, >£25m if all piroxicam and diclofenac prescriptions are switched to meloxicam	Not reported

²⁷ See section 4.1.2, MSD submission.

²⁸ See section 4.1.2, Pfizer & Searle submission.

We have attempted to estimate the total cost impact of Cox-II inhibitors on the NHS, based on total drug expenditure, total costs incurred by the use of each competing product and a range of prevalence estimates for OA and RA. We recognise the difficulties in deriving a reliable estimate due to the lack of comparable data, but the following results are consistent, given the assumptions stated. It should be noted that these results may be overestimates as some of the Cox-II inhibitors have established markets and have been in use for a long time, therefore the baseline expenditure may be slightly higher than reported here.

Table 4.12 shows the daily and annual cost of each drug per OA patient. Annual costs are calculated with the assumption that each drug will be used for only 180 days in a year. The unit costs are taken as those reported by each manufacturer and for generic NSAIDs an average figure of £0.30 is used. This figure is consistent across different submissions and reflects a weighted average cost according to the market shares of different products. In the high cost scenario the prevalence of OA was assumed to be 1,750,000, which is derived from the GP Morbidity Statistics, whereas a more conservative estimate, by the Arthritis and Rheumatism Council Epidemiology Unit (1,350,000), was applied in the low-cost scenario. Incremental costs compared with the generic NSAIDs are reported in a separate column.

Table 4.12 Cost impacts for OA based on drug costs only

	Drug costs only ²⁹		Low cost scenario ³⁰ (£)		High cost scenario ³¹ (£)	
	Daily	Annual	Total annual drug budget	Δ from gnr ³² NSAID	Total annual drug budget	Δ from gnr NSAID
Rofecoxib	0.79	142.2	188,415,000	116,865,000	248,850,000	154,350,000
Celecoxib	0.61	109.8	145,485,000	73,935,000	192,150,000	97,650,000
Meloxicam	0.33	59.4	78,705,000	7,155,000	103,950,000	9,450,000
Etodolac	0.52	93.6	124,020,000	52,470,000	163,800,000	69,300,000
NSAID (generic)	0.3	54.0	71,550,000	0	94,500,000	0

Considering only the drug costs is clearly not the most accurate way of estimating the financial implications of pharmaceutical products. If a similar efficacy is established, one way to assess the cost impact could be utilising the total costs (shadow costs) incurred by using these drugs, which would also include the cost of treating adverse events caused by the treatment (iatrogenic costs).

Total costs incurred by the use of rofecoxib and celecoxib were readily available in the MSD and Pfizer & Searle submissions. For NSAIDs, estimated total costs were similar in these two submissions (£0.59 in MSD, 0.65 in Pfizer & Searle), therefore a round estimate of £0.60 was used in the

²⁹ 180 days of treatment in one year is assumed.

³⁰ In low cost scenario, the total number of OA patients is assumed to be 1,325,000 (source: Arthritis and Rheumatism Council Epidemiology Unit)

³¹ In low cost scenario, the total number of OA patients is assumed to be 1,750,000 (derived from GP Morbidity Statistics)

³² gnr: generic

analysis. This implies an iatrogenic cost factor of “2” for NSAIDs, which is consistent with the literature.

The total cost estimates for meloxicam were obtained from the decision tree in the Boehringer Ingelheim submission (£146/180=0.81). This model estimates the total daily cost for rofecoxib as £0.92 (£166/180=0.92), which is consistent with the MSD estimates. However, a total daily cost of £0.81 for meloxicam implies an iatrogenic cost factor of “2.45” which is higher than the one used for NSAIDs³³.

There were no estimates available for etodolac to calculate the total costs, as the Shire submission did not include a comprehensive economic evaluation. Therefore the only way to estimate the total costs for etodolac was to use the iatrogenic cost factors reported elsewhere in the literature. There were two estimates reported; one of them was in the UK context (103) and reported an iatrogenic cost factor of 1.84 to 1.93 for etodolac, whereas the other study estimated this as 2.12 in France (101). The cost impact analysis carried out in this report used the more conservative figure (1.84) and calculated the total cost of etodolac as £172.20 per patient per annum. Based on the total costs of each of the drugs, incremental costs for switching to new NSAIDs for OA treatment are given in Table 4.13. Clearly, none of the drugs will be able to expand its market share to 100%, therefore the highest cost estimates will never be realised.

Although this analysis does not directly address the potential cost-savings due to reduced use of GPAs, these savings are implicit in the total cost (shadow cost) calculations.

Table 4.13 Cost impact for OA based on all costs associated with drug use

	All costs ³⁴		Low cost scenario (£)		High cost scenario (£)	
	Daily	Annual	Total expenditure	Δ from gener. NSAID	Total expenditure	Δ from gener. NSAID
Rofecoxib	0.91 ³⁵	163.8	217,035,000	73,935,000	286,650,000	97,650,000
Celecoxib	0.825 ³⁶	148.5	196,762,500	53,662,500	259,875,000	70,875,000
Meloxicam	0.81 ³⁷	145.8	193,185,000	50,085,000	255,150,000	66,150,000
Etodolac	0.96 ³⁸	172.2	228,196,800	85,096,800	301,392,000	112,392,000
NSAID (generic)	0.6 ³⁹	108.0	143,100,000	0	189,000,000	0

³³ The same model calculated the iatrogenic cost factor of 5.67 for diclofenac and 8.75 for piroxicam.

³⁴ This includes all the costs associated with drug use ie treatment of adverse events

³⁵ Taken from MSD submission (scenario 1).

³⁶ Taken from Pfizer & Searle submission (£148,591/180=£0.825)

³⁷ Calculated from decision tree in Boehringer Ingelheim submission (£146/180=0.81). This model estimates the shadow cost for rofecoxib as £0.92 (£166/180=0.92), which is consistent with MSD estimates.

³⁸ Iatrogenic cost factor of 1.85 is assumed (based on Knill-Johns(103))

³⁹ The shadow cost estimates for generic NSAIDs are consistent in different models. MSD model: £0.59 and Pfizer & Searle model: £0.65 (£118,140/180).

The current evidence suggests that meloxicam, together with the other Cox II inhibitors, has similar efficacy and apparently a better GI safety profile compared with standard NSAIDs. Therefore a higher iatrogenic cost factor for meloxicam than for NSAIDs contradicts the findings of the systematic review, if we assume meloxicam causes no additional adverse effects (and therefore costs) on other systems of the body. It would therefore make sense to assume that the iatrogenic cost factor for meloxicam is better than or equal to that of NSAIDs, which we have taken as a value of “2”. If we take this to be the case, the total daily cost for meloxicam will be £0.66 instead of £0.81, and switching all NSAID prescriptions for OA treatment to meloxicam would cost the NHS around £14,310,000 -£18,900,000 (in contrast to the figures reported in Table 4.13).

NSAID use in RA treatment involves higher doses, and therefore possibly more adverse events at higher total costs. The Pfizer & Searle submission estimated the total costs of celecoxib treatment at £1.09 (£0.88 for drug costs and £0.21 for net event costs) and £0.69 for generic NSAIDs (£0.34 for drug costs and £0.36 for net event costs). Cost impact estimates based on these values are given in Table 4.14. Rofecoxib is not licensed for RA and there is no data for meloxicam and etodolac.

Table 4.14 Cost impact estimates for RA (based on Pfizer & Searle submission)

	Daily costs (£)	Low cost scenario ⁴⁰ (£)		High cost scenario ⁴¹ (£)	
		Total annual drug budget	Δ from generic NSAID	Total annual drug budget	Δ from generic NSAID
Drug costs only					
Celecoxib	0.88	39,600,000	24,480,000	79,200,000	48,960,000
NSAID (generic)	0.34	15,120,000	0	30,240,000	0
All costs associated with drug use					
Celecoxib	1.09	49,050,000	17,820,000	98,100,000	35,640,000
NSAID (generic)	0.69	31,230,000	0	62,460,000	0

If we assume no difference in the dosage and safety profile of NSAID treatment across all arthritis patients (OA and RA), the additional costs of treating RA patients could be estimated by simply adding the RA patients to the first analysis. The estimated impact of wider use of Cox-II inhibitors in the treatment of RA, based on the figures used in OA impact analysis, is given in Table 4.15.

⁴⁰ In low cost scenario, the total number of RA patients is assumed to be 250,000

⁴¹ In high cost scenario, the total number of RA patients is assumed to be 500,000.

Table 4.15 Cost impact of Cox-II inhibitors for RA (based on OA treatment costs)

	Low cost scenario (£)			High cost scenario (£)	
Drug costs only					
	Annual (£)	Total annual drug budget	Δ from generic NSAID	Total annual drug budget	Δ from generic NSAID
Rofecoxib	142.2	35,550,000	22,050,000	71,100,000	44,100,000
Celecoxib	109.8	27,450,000	13,950,000	54,900,000	27,900,000
Meloxicam	59.4	14,850,000	1,350,000	29,700,000	2,700,000
Etodolac	93.6	23,400,000	9,900,000	46,800,000	19,800,000
NSAID (generic)	54.0	13,500,000	0	27,000,000	0
All costs					
	Annual (£)	Total annual drug budget	Δ from generic NSAID	Total annual drug budget	Δ from generic NSAID
Rofecoxib	163.8	40,950,000	13,950,000	81,900,000	27,900,000
Celecoxib	148.5	37,125,000	10,125,000	74,250,000	20,250,000
Meloxicam	145.8	36,450,000	9,450,000	72,900,000	18,900,000
Etodolac	172.2	43,056,000	16,056,000	86,112,000	32,112,000
NSAID (generic)	108.0	27,000,000	0	54,000,000	0

Risk Groups

It is difficult to estimate the likely cost impact if the Cox-II inhibitors were made available for only certain high-risk groups. Most studies report the proportion of patients with previous GI events around 8%(13). However, these data come from the trial settings and may not reflect the real distribution of patients in the community. According to GP morbidity statistics 56% of all OA patients and 41% of all RA patients are over 65 and 30% of all OA patients and 17% of all RA patients are over 75. The corresponding figures from the Arthritis and Rheumatism Council Epidemiology Unit (ARC) were 59% (over 65) and 32% (over 75) for OA and 48% and 25% for inflammatory arthritis (including juvenile chronic arthritis and ankylosing spondylitis but excluding gout). Mid-estimates of those two are used in the following cost impact analysis.

Table 4.16 Proportion of patients over 65 and 75 years of age in all OA population

	OA		RA	
	Over 65	Over 75	Over 65	Over 75
GP morb stats	56%	30%	41%	17%
ARC data	59%	32%	48%	25%
NICE	58%	31%	45%	21%

Adding a further 8% of the remaining patients (patients with previous GI events), the cost impact of Cox-II inhibitors can be estimated as a percentage of the previous total cost estimations (Table 4.17). According to these, if >65 and patients with previous GI events are targeted, the total annual expenditure of £35.4m-£86.6m could be expected over and above current

spending. However the corresponding figures will be £20,9m-£50.7m if the age group selected was >75.

It should be noted that because of lack of data this analysis assumes constant relative risk reduction across different risk groups. As there will be more GI events averted in high-risk patients, the differences between shadow costs of Cox- II inhibitors and standard NSAIDs will be smaller, therefore the estimated cost impact presented in Table 4.17, may be an overestimate.

Table 4.17 Cost impact analysis for risk groups

	% of all	Low (£)	High (£)
All Osteoarthritis	100.0	50,085,000⁴²	112,392,000⁴³
Previous GI events and >65	61.4 ⁴⁴	30,752,190	69,008,688
Previous GI events and >75	36.5	18,281,025	41,023,080
All Rheumatoid Arthritis	100.0	9,450,000⁴⁵	35,640,000⁴⁶
Previous GI events and >65	49.4	4,668,300	17,606,160
Previous GI events and >75	27.3	2,579,850	9,729,720

⁴² The lowest estimate reported in Table 4.13.

⁴³ The highest estimate reported in Table 4.13.

⁴⁴ Includes patients with previous GI event and also >65. (ie $58+(100-58) \times 0.08=61.36$)

⁴⁵ The lowest estimate reported in Table 4.14 and Table 4.15.

⁴⁶ The highest estimate reported in Table 4.14 and Table 4.15.

5. Discussion

For patients with OA and RA, NSAIDs are the mainstay of care. Well-established limitations of NSAID therapy, however, include the risk of developing significant injury to the upper gastrointestinal tract. The purpose of this review was to assess the relative effectiveness of Cox-II inhibitors (celecoxib, etodolac, meloxicam and rofecoxib) with other NSAIDs for the management of patients with OA and RA.

5.1. Summary of effectiveness evidence

This review firstly provides evidence that the Cox-II inhibitors have equivalent efficacy to that of other NSAIDs in terms of their ability to reduce pain and improve physical and global function of both OA and RA patients(34). The second finding of this review was that there is evidence that the four Cox-II inhibitors are effective in reducing the incidence of GI adverse events of OA and RA patients compared to NSAID therapy. When these two findings are put together, it can be concluded that there is evidence to support the use of these four Cox-II inhibitors in preference to NSAIDs for the management of OA and RA.

No 'head-to-head' trials directly comparing the four Cox-II inhibitors in RA & OA were identified. Nevertheless indirect comparisons (i.e. the effect of the four drugs relative to NSAIDs) indicated little difference in either efficacy outcomes or adverse event outcomes. For example, odds ratios from meta-analysis for PUBs were 0.33 (95% CI: 0.24-0.46) for celecoxib 200-400 mg/day, rofecoxib 12.5-50 mg/day, 0.31 (95% CI: 0.24-0.40), meloxicam 7.5-15 mg/day, 0.48 (95% CI: 0.26-0.88) and etodolac 600-1000mg/day, 0.20 (95% CI: 0.07-0.53) versus NSAIDs. However, conclusions from such indirect comparisons should be treated with caution. There are potentially differences across the trials in the baseline risk of the patients, use of concomitant therapies, choice and dosage of comparator NSAIDs, and method of outcome assessment. Therefore a definitive conclusion on the relative effectiveness of these four drugs cannot be made from the evidence base of this review. In other words, there is no overall evidence to suggest that any one of the for Cox-II inhibitors in this review is clinically superior to the others.

A recent systematic review has examined the association between NSAIDs and adverse outcomes, identified a number of so-called patient characteristics that are 'risk factors' i.e. increase the risk of adverse events (11). This review concluded that these risk factors should include advanced age (i.e. >65 years), higher doses of treatment and a history of peptic ulcer disease. In addition, Fries and colleagues, have determined a risk calculator for adverse events with NSAIDs based on combination of a number of risk factors i.e. higher age, use of prednisolone, previous NSAID GI side effects, prior GI hospitalisation, level of disability, and NSAID dose (107). The higher the Fries risk score (based on the prevalence of the risk factors) the greater the probability of adverse events. A number of trials, particularly those undertaken more than 3-5 years ago, have tended to exclude such high-risk patients. For example, many of the trials have been conducted in adults aged less than 65

years. It is therefore not possible to comment on the relative impact of the Cox-II inhibitors in high-risk individuals within such trials. Moreover given the relatively small size of the majority of trials in this review, it is likely that they would be underpowered to undertake a high-risk subgroup analysis. Two studies that did undertake a high-risk subgroup analysis were identified within this review. The first was undertaken by the VIGOR study, a large randomised trial of rofecoxib versus NSAIDs (MSD submission). The second was based on a subgroup analysis undertaken of a meta-analysis of celecoxib versus NSAID trials (Pfizer submission). In the VIGOR trial... (in commercial confidence). Thus, although at greater risk of adverse events, there appears to insufficient evidence from this review to comment on the relative impact of the Cox-II inhibitors in high-risk patients.

Two particular related issues regarding the potential use of the Cox-II inhibitors arose within the evidence base of this review. The first was a possible increase in the risk of cardiovascular adverse events by replacing NSAIDs with Cox-II inhibitors. It has been hypothesised that Cox-II inhibitors might increase the risk of cardiovascular thromboembolic events via inhibition of vascular prostacyclin synthesis without a corresponding inhibition of platelet thromboxane. In other words, the Cox-II inhibitors may lose the cardio protective benefit associated with the Cox I action of the other NSAIDs. There is some support for this hypothesis from the recent large VIGOR trial that reported an increase in number of myocardial infarctions (MI) (0.3%) compared with the NSAID comparator naproxen (0.1%). However, this increase in risk was relatively small and principally in those patients who were not on low dose aspirin, but who would have met the criteria for cardio-prophylaxis. In the similarly large CLASS trial of celecoxib compared to NSAID, there was no evidence in cardiovascular events with NSAIDs. Moreover the majority of trials in this review did not report the adverse events in a disaggregated way or assess cardiovascular events. Therefore, at this time, there remains insufficient evidence to be able to definitely come to a conclusion on the effect of Cox-II inhibitors on cardiovascular adverse events. The second issue is over the concomitant use of aspirin with the Cox-II inhibitors. In the CLASS trial, the rate of ulcer complications with celecoxib was greater in those individuals also taking low dose (< 75mg/day) aspirin (2.6%) compared to those not taking aspirin (1.3%). In summary, there may a rationale for individuals on Cox-II inhibitors to not take aspirin unless they have a cardiovascular history and in such cases, low dose aspirin (up to 75mg/day) would be recommended. There is a need for further clinical studies to clearly define the value of Cox-II inhibitors in patients on low-dose aspirin treatment.

5.2. Summary of the economic evidence

The current evidence on cost-effectiveness of Cox-II inhibitors remains inconclusive. Economic models developed by manufacturers generate favourable outcomes for the Cox-II inhibitors versus standard NSAIDs, including cost-savings, for all OA and RA patients, (in confidence). There are no published economic evaluations for Cox-II inhibitors in the UK context, other than the one meloxicam study.

The Pfizer & Searle submission reports a “cost per GI event saved” as low as £749. However, the definition of GI event is broad and includes milder side effects like diarrhoea. Cost per PUB may be a more informative outcome than cost per GI event averted, but the definition of PUB is not always straightforward. They are either detected by endoscopies as non-symptomatic (or silent) ulcers and therefore the clinical significance of them might be in doubt, or by indirect methods such as testing for occult blood in stool to provide a rather soft end point (108). Peterson and Cryer (90) argue that endoscopically diagnosed ulcers, defined as mucosal breaks of ≥ 3 mm in diameter with unequivocal depth, are clinically unimportant and may not be appropriate surrogate measures to evaluate the safety of NSAIDs. Industry submissions reported cost per symptomatic PUBs averted as in the range of £3,800 and £10,759, with the exception of £211,700 for low risk patients in the Shire submission. The corresponding figure in the CCOHTA report is ... (in confidence).

The upper range of cost per LYG values in the industry submissions range between £6,842 and £15,647. In the CCOHTA report ...(in confidence)

There are two cost per QALY estimates, both coming from Canadian studies... (in confidence).

When risk groups are considered, there seems to be less conflict between the submissions as most evaluations generate more favourable results for these high-risk groups. (Despite this, the definition of high-risk remains unclear.) In the Shire submission, high-risk groups are defined as >75 years of age and with prior history of ulcer and/or GI bleeding (based on Silverstein et al(15)), whereas in the VIGOR study, being over 65 was defined as a risk factor. Clearly, the definition of the risk criteria remains as an important factor in determining the cost-effectiveness results.

The Pfizer & Searle submission developed a scoring system to explain the potential relationship between identified risk factors and the cost effectiveness ratios, which is based on the earlier work by Fries(107). This model shows a steep increase in cost effectiveness ratios for risk scores less than 11 to reach £20,000 per LYG for the risk score of 7. (A score of 7 can represent all patients with a history of serious GI event, or all patients over 55 years of age regardless of their history.) However this is a linear scale and may be overestimating the risks associated with the lower age groups.

The effectiveness review concludes that there is currently insufficient evidence to support a superior safety profile in high-risk RA and OA patients compared with all RA and OA patients. However, the greater probability of developing GI events in such high-risk patients, means that the *absolute* number of GI events averted is likely to be greater for those sub groups. Therefore, despite the remaining need for clearer definition for risk groups, the use of Cox-II inhibitors in high-risk patients with OA and RA may be justified in the light of reviewed cost-effectiveness studies. However, there is a lack of consistent evidence for the use of Cox-II inhibitors in all arthritis patients, with

few studies and conflicting cost-effectiveness ratios. In addition it is not possible to draw conclusions about the cost effectiveness of one Cox-II inhibitor over another. There is a further need for methodologically sound cost-effectiveness studies, possibly using the data from 'head to head' trials, and incorporating quality of life outcomes.

5.3. Limitations of the evidence base

There is a large evidence base of randomised controlled trials of the effectiveness of Cox-II inhibitors in OA and RA patients compared to NSAIDs. However, there are a number of issues regarding this evidence base:

- There are currently no 'head to head' trials of the four Cox-II inhibitors assessed within this review. Without trials that directly compare these drugs for OA and RA, it is not possible to come to a definite conclusion on their relative effectiveness.
- The lack of standardisation on outcome measures (particularly for efficacy outcomes) and variability in the methods of reporting outcomes, make comparing study results difficult. Given this, it was not possible to undertake a meta-analysis of efficacy outcomes in this review.
- The length of follow-up of trials has in general been relatively short i.e. 4 to 6 weeks, although there were some exceptions to this including the VIGOR and CLASS trials. The only Cox-II inhibitor with trial based follow up in excess of 1 year was etodolac. The issue of long-term follow up is particularly important when assessing drug safety. The results of benefits of this review need to be considered in this context. Long-term follow up in trial settings is often difficult and there may be therefore a role for well collected long-term observational data.
- Although most of the studies in this review were randomised controlled trials and many with double blinding, the quality of reporting of the majority of these trials was poor. This potentially limits the validity and relevance of the findings.
- Finally, in the sample sizes of many of these trials were relatively small and therefore likely to be underpowered to detect small differences that may have existed in some outcomes.

Many of these issues around the quality of trials in NSAIDs have been discussed in previous reviews (4;34)

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1. Appendices

Appendix A: Epidemiology of arthritis

Data from 'Morbidity statistics from general practice: fourth national study 1991-1992'

Epidemiology and service use for OA (per 10 000 person years at risk)

Age band	0-4	5-15	16-24	25-44	45-64	65-74	75-84	85 +
Incidence	0	1	6	49	325	560	676	645
Prevalence	1	1	10	69	559	1038	1370	1444
M/F ratio	-	1.0	1.2	0.7	0.7	0.7	0.6	0.6
Consultations	1	1	15	103	1056	1893	2637	2699

Epidemiology and service use for RA (per 10 000 person years at risk)

Age band	0-4	5-15	16-24	25-44	45-64	65-74	75-84	85 +
Incidence	0	1	3	11	24	29	23	25
Prevalence	1	3	6	21	71	111	101	71
M/F ratio	-	-	0.2	0.4	0.5	0.5	0.4	0.2
Consultations	1	3	10	57	225	313	268	107

Appendix B: Revised ARA criteria for the classification of rheumatoid arthritis, 2000

For classification purposes, a patient is said to have RA if he or she has satisfied at least 4 of the following 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable RA is not to be made.

1. **Morning stiffness**
Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2. **Arthritis of 3 or more joint areas**
At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician; the 14 possible joint areas are right or left proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, wrist, elbow, knee, ankle, and metatarsophalangeal (MPT) joints.
3. **Arthritis of hand joints**
At least 1 area swollen (as defined above) in a wrist, MCP or PIP joint.
4. **Symmetric arthritis**
Simultaneous involvement of the same joint areas (see 2 above) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5. **Rheumatoid nodules**
Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
6. **Serum rheumatoid factor**
Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.

Radiographic changes

Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

Appendix C: Full list of NSAIDs from BNF 40: September 2000 (9)

Name (Trade)	Manufacturer	UK Licence?	Costs	Indications	Dosage
Aceclofenac (Preservex)	UCB Pharma	Yes		Pain and inflammation in RA and OA	
Acemetacin (Emflex)	Merck	Yes		Pain and inflammation in rheumatic disease	
Azapropazone (Rheumox)	Goldsheild	Yes		Use in RA ONLY when other NSAIDs have been tried and failed.	
Celecoxib (Celebrex)	Searle & Pfizer	Yes	100mg, net price 60= £18.34	Pain and inflammation in OA and RA	200mg daily increased if necessary to maximum of 200mg twice daily
Dexketoprofen (Keral)	Menarini	Yes		Short-term treatment of mild to moderate pain	
Diclofenac solution	various	Yes		Pain and inflammation in RA	
Diflunisal (Dolobid)	MSD	Yes		Pain and inflammation in rheumatic disease	
Etodolac (Lodine)	Monmouth	Yes	Tablets 600mg 30 = £15.50	Pain and inflammation in rheumatoid arthritis and osteoarthritis	600mg daily; not recommended for children
Fenbufen	Various	Yes		Pain and inflammation in rheumatic disease	
Fenoprofen (fenopron)	Typharm	Yes		Pain and inflammation in rheumatic disease	
Flurbiprofen (Froben)	Knoll	Yes		Pain and inflammation in rheumatic disease	
Ibuprofen	Various	Yes		Pain and inflammation in rheumatic disease	
Indometacin	various	Yes		Pain and moderate to severe inflammation in rheumatic disease	
Ketoprofen	various	Yes		Pain and mild inflammation in	

				rheumatic disease	
Mefanamic acid	various	Yes		Mild to moderate pain in RA and OA	
Meloxicam (Mobic)	Boehringer Ingelheim	Yes	tablets 7.5mg 30 = £10.00; 15mg 30 = £13.90. suppositories 7.5mg 12 = £4.00; 15mg 12 = £6.00	Pain and inflammation in rheumatic disease; exacerbation of osteoarthritis (short term) ankylosing spondylitis	By mouth for osteoarthritis, 7.5mg daily with food, increased if necessary to max. 15mg once daily; by mouth for rheumatoid arthritis and ankylosing spondylitis, 15mg once daily with food (7.5mg in the elderly) By rectum; same doses by suppository Not recommended for children under 15.
Nabumetone	various	Yes		Pain and inflammation in OA and RA	
Naproxen	various	Yes		Pain and inflammation in rheumatic disease	
Phenylbutazone (Butacote)	Novartis	Yes		Ankylosing spondylitis	
Piroxicam	various	Yes		Pain and inflammation in rheumatic disease	
Rofecoxib (Vioxx)	Merck Sharpe Dohme	Yes	Tablets 12.5mg & 25mg 28 = £21.58; Suspension 12.5mg/5ml & 25mg/5ml 150ml=£23.12	Pain and inflammation in osteoarthritis	12.5mg daily; increased if necessary to max. 25mg once daily; not recommended for children.
Sulindac (Clinoril)	MSD	Yes		Pain and inflammation in rheumatic disease	
Tenoxicam (Mobiflex)	Roche	Yes		Pain and inflammation in rheumatic disease	
Tiaprofenic acid	Various	Yes		Pain and inflammation in rheumatic disease	

Appendix D: Search strategies

Medline 1966 – June week 4 2000 (via OVID, Biomed)

- #1 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenasell).ti, ab
- #2 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenasell).ti, ab
- #3 (cox-2 or cox2 or cox-II or coxII).ti, ab
- #4 (rofecoxib or vioxx or MK-0966).mp
- #5 (celecoxib or celebrex or SC-58635).mp
- #6 (meloxicam or mobic).mp
- #7 (etodolac or lodine or ultradol).mp
- #8 *Cyclooxygenase inhibitors/
- #9 *Etodolac/
- #10 or/1-9
- #11 arthrit\$ or osteoarthrit\$
- #12 exp *Arthritis/
- #13 11 or 12
- #14 10 and 13

combined with Cochrane rct filter and NHS CRD economic evaluation filter.

Cochrane Controlled Trials Register (CCTR) (Issue 2: 2000)

- #1 cyclooxygenase*
- #2 "cyclo oxygenase*"
- #3 cox*
- #4 rofecoxib or vioxx
- #5 celecoxib or celebrex
- #6 meloxicam or mobic
- #7 etodolac or lodine or ultradol
- #8 cyclooxygenase-inhibitors:ME
- #9 etodolac:ME
- #10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
- #11 arthrit* or osteoarthrit*
- #12 arthritis*:ME
- #13 #11 or #12
- #14 #10 and #13

Embase (1980 – July 2000, via Silverplatter)

- 1 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenasell) in ti, ab
- 2 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenasell) in ti, ab
- 3 (cox-2 or cox2 or cox-II or coxII) in ti, ab
- 4 (rofecoxib or vioxx or MK-0966) in ti, ab, mn, tn
- 5 (celecoxib or celebrex or SC-58635) in ti, ab, mn, tn

- 6 (meloxicam or mobic) in ti, ab, mn, tn
- 7 (etodolac or lodine or ultradol) in ti, ab,mn, tn
- 8 "cyclooxygenase-2-inhibitor"/ all subheadings
- 9 "cyclooxygenase-2"/ all subheadings
- 10 "celecoxib"/ all subheadings
- 11 "meloxicam"/ all subheadings
- 12 "etodolac"/ all subheadings
- 13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
- 14 arthrit*
- 15 osteoarthrit*
- 16 (arthrit* or osteoarthrit*) in ti, ab
- 17 explode "arthritis"/ all subheadings
- 18 #16 or #17
- 19 #13 and #18

Appendix E: Abstract selection form

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

Review of the clinical effectiveness and cost effectiveness of cox-II inhibitors and their use in arthritis

ABSTRACT SELECTION FORM

Ref no:

Journal/vol/part:

Year:

Reviewer:

	Yes	No	Can't tell	Comments
Design: 1. Prospective randomised controlled trial or 2. Economic Evaluation (cost minimisation, cost effectiveness, cost utility or cost benefit)				
Population: Patients with rheumatoid or osteo arthritis				
Intervention: Cox-IIs – rofecoxib, celecoxib, etodolac or meloxicam				
Outcomes One or more of the following 1. Pain 2. Joint movement 3. Patient assessment of disease Adverse effects 1. Death 2. Major bleeding 3. Minor bleeding 4. GI adverse events				

Outcomes (state the method used, when appropriate)

- | | | |
|-------------------------------|-------------------------------------|-----------------------------------|
| Pain | <input type="radio"/> | Side effects: |
| Physical function | <input type="radio"/> | Gastrointestinal |
| <input type="radio"/> | | |
| Range of motion | <input type="radio"/> | Other |
| <input type="radio"/> | | |
| Patient global assessment | <input type="radio"/> | Global assessment of tolerability |
| <input type="radio"/> | | |
| Clinicians' global assessment | <input type="radio"/> | |
| Quality of life | <input type="radio"/> | |
| Other | <input type="radio"/> <i>please</i> | |
| <i>specify</i> | | |

B. Quality Assessment

(Please fill out the form to calculate the JADAD score, see page vi)

C. Study design

Type of trial (crossover or parallel)

D. Population

Inclusion criteria

.....

Exclusion criteria

.....

	Intervention			Control
	Rx 1	Rx 2	Rx 3	
Sex mix (male/ total)				
Mean age				
Duration of disease				

E. Intervention

	Drug (daily dose)	Drug dose / MDD ⁴⁷ %	No of patients Randomised
A			
B			
C			
D			

Duration of treatmentdays / weeks / months (circle the appropriate one)

Washout period

Common treatments available to both groups.....

F. Dropouts

	Number of patients enrolled	Number of patients completed the trial	%
Study group			
Control group			

⁴⁷ MDD= Maximum daily dose

G. Outcomes (*Please report intention-to-treat values*)

	Outcome measures	Rx 1	Rx 2	Rx 3
Pain				
Physical function				
Range of motion				
Patient global assessment				
Clinicians' global assessment				
Global assessment of tolerability				
Other <i>please specify</i>				
.....				
..... ...				

Comments

.....

H. Adverse effects

Please tick as appropriate

All adverse effects

Adverse effects leading to withdrawal

	Rx 1		Rx 2		Rx 3	
	n	%	n	%	n	%
1. Gastrointestinal						
• Minor gastrointestinal (dyspepsia, abdominal pain, diarrhoea etc)						
• PUB ⁴⁸						
• Other gastrointestinal						
Discontinuation due to GIS adverse effects						
Total Gastrointestinal						
2. Cardiovascular system						
• Oedema						
• Hypertension						
• Myocardial Infarction						
3. Other systems (please specify)						
4. Death						
TOTAL (severe side effects)⁴⁹						
TOTAL (all causes)						

Additional comments:

.....
.....

I. Reviewer's Notes

⁴⁸ PUB (perforations, ulcerations, bleedings) includes: duodenal ulcer, reactive/perforated duodenal ulcer, gastric ulcer, aggravated peptic ulcer, gastric bleeding (haemorrhagic duodenal and peptic/gastric ulcer) haematemesis, melaena.

⁴⁹ If stated separately

Appendix G

Excluded studies

Celecoxib

- (109) not an rct
- (110) only trial comparing celecoxib & rofecoxib but in dental pain
- (111) healthy participants
- (112) healthy participants
- (113) healthy participants
- (46) excluded from effectiveness analysis: reported adverse events only
- (47) excluded from effectiveness analysis: reported adverse events only
- (48) excluded from effectiveness analysis: reported adverse events only

Rofecoxib

- (110) only trial comparing celecoxib & rofecoxib but in dental pain
- (53) excluded from effectiveness analysis: reported adverse events only
- (58) excluded from effectiveness analysis: reported adverse events only
- (114) not rofecoxib

Meloxicam

- (115) intramuscular administration of meloxicam
- (116) not an rct
- (117) excluded from effectiveness analysis: reported adverse events only
- (61) excluded from effectiveness analysis: concomitant therapy
- (62;63;69) excluded from effectiveness analysis: study duration too short
- (117) intramuscular and suppository administration of meloxicam

Etodolac

- (89) excluded from effectiveness analysis; low doses of drug
- (88) excluded from effectiveness analysis; low doses of drug
- (85) excluded from effectiveness analysis; low doses of drug
- (84) excluded from effectiveness analysis; low doses of drug
- (83) excluded from effectiveness analysis; low doses of drug
- (79) excluded from effectiveness analysis; low doses of drug
- (77) excluded from effectiveness analysis; low doses of drug
- (75) excluded from effectiveness analysis; low doses of drug
- (76) excluded from effectiveness analysis; low doses of drug
- (73) excluded from effectiveness analysis; low doses of drug
- (74) excluded from effectiveness analysis; low doses of drug
- (86) excluded from effectiveness analysis; low doses of drug
- (92) excluded from effectiveness analysis; small no. of participants
- (81) excluded from effectiveness analysis; small no. of participants
- (82) excluded from effectiveness analysis; small no. of participants
- (80) excluded from effectiveness analysis; small no. of participants
- (87) excluded from effectiveness analysis; small no. of participants
- (72) excluded from effectiveness analysis; small no. of participants
- (118) etodolac vs. etodolac

COX-2 INHIBITORS ASSESSMENT REPORT ADDENDUM: February 2001

Pharmacia and Pfizer submitted a number of unpublished studies as commercial in confidence. These data have been removed from this assessment report addendum to enable publication on the website. The Appraisal Committee had full access to these data prior to their meeting of 26th April.

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1. AIM OF THE REVIEW

To establish the relative clinical efficacy, cost effectiveness and safety of celecoxib, rofecoxib, etodolac and meloxicam in the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA) by systematic review of available evidence.

2. METHODS

2.1 SEARCH STRATEGY

The search strategy developed for the original review was re-run in Medline (June week 4 – December week 4 2000), Embase (July – December 2000) and the Cochrane Controlled Trials Register (Issue 4:2000) to retrieve recently indexed studies (see Appendix I).

As per usual internal NICE searching methods, the bibliographies of the submissions from manufacturers/sponsors were scanned to retrieve any additional studies papers not located using standard search strategies.

In the original searching, two Cochrane reviews (1;2) on NSAIDs for hip and knee OA were retrieved as stated in the original report. These studies have subsequently been included in this review.

2.2. INCLUSION CRITERIA

2.2.1 INTERVENTIONS

Randomised controlled trials (RCTs) were accepted which evaluated any of the four study drugs using UK licensed doses. Studies were excluded if concomitant therapy was used which would confound interpretation of the results.

TABLE 1: LICENSED DOSES OF STUDY INTERVENTIONS

INTERVENTION	OA	RA
celecoxib (Celebrex)	200mg daily max 400mg	200-400mg daily
rofecoxib (Vioxx)	12.5mg daily max 25mg	not licensed
meloxicam (Mobic)	7.5mg daily max 15mg	15mg daily
etodolac (Lodine)	600mg daily	600mg daily

2.2.2 POPULATION

Patients with OA or RA with no restrictions for age or sex.

2.2.3 STUDY DESIGN

Prospective RCTs of parallel design in which the study drugs were compared to either placebo or another NSAID. Open trials were included, if their results

could be interpreted with respect to their inherent potential for bias. No exclusions on the basis of language of publication were made.

2.2.4 COMPARATORS

Studies were accepted that compared any of the study drugs to either placebo or other NSAIDs.

2.2.5 OUTCOME MEASURES

Studies were included if any accepted method to assess disease severity or progression was used. Data were also collected on the incidence and severity of adverse events (AEs) associated with therapy, the number of gastrointestinal AEs (GI AEs) and the number of withdrawals due to total AEs and GI AEs. In most cases the restricted sample sizes of RCTs make it unlikely that rarer ADRs would be detected and therefore data on the number of perforations, ulcers and bleeds (PUBs) were collected only from studies with sufficiently large sample sizes. Ulcers detected by endoscopy were not pooled with ulcers presenting clinically.

2.3 EXCLUSION CRITERIA

Studies were excluded that had 50 or less patients in each arm, duration of treatment of less than four weeks or used concomitant intra-articular corticosteroid therapy.

2.4 STUDY SELECTION AND DATA EXTRACTION

Two reviewers independently ascertained whether each study met the inclusion criteria for the review and a double abstraction process was undertaken. Any discrepancies were resolved by discussion and where this was not possible the authors of the study were contacted for clarification. Duplicate publications of the same study were considered in tandem with the original publication.

2.5 QUALITY ASSESSMENT

Where possible, the Jadad scale was used (3) to assign an overall quality score to each study. In many cases the trial reporting did not permit a quantitative assessment of the quality of the trial and therefore the quality score was not used to stratify the analysis.

2.6 DATA ANALYSIS

The initial aim of the review was to statistically pool the results of the individual studies for each of the interventions to produce an overall estimate of effect. However this was not possible for efficacy data, due to the heterogeneities of both design and outcome measures used as well as lack of standardisation of the methods of reporting.

Where possible data from intention to treat (ITT) analysis was used and it was not combined with other data. Efficacy data from OA and RA trials were considered separately, whilst AE data were pooled across all trials. Study results were pooled using standard meta-analytical methodology (4). The data were analysed using a fixed effect model except in those circumstances

where there was evidence of statistical heterogeneity in which case the results were pooled using a random effects model. All data analysis was undertaken using RevMan version 4.1.

3. RESULTS

3.1 LITERATURE SEARCHES

The results of the literature searches are included in Table 2. This review includes an additional 24 studies which were not included in the original report.

TABLE 2: RECOVERY STATISTICS FOR LITERATURE SEARCHES

INTERVENTION	EXCLUDED	INCLUDED	ADDITIONAL STUDIES	NUMBER OF PATIENTS
celecoxib	7	15	9	19,193
rofecoxib	3	17	6	17,886
meloxicam	17	9	2	20,592
etodolac	41	12	7	4060
TOTAL	68	53	24	61,731

3.2 SUMMARY OF EXCLUDED STUDIES: SEE APPENDIX II

3.3 DETAILS OF INCLUDED STUDIES: SEE TABLES 3-10

Additional studies that have been included in this updated systematic review are underlined in the tables.

3.4 SUMMARY OF INDIVIDUAL STUDY RESULTS: SEE TABLES 11-25

KEY TO TABLES: N= number of patients; OMs= outcome measures; SS= statistically significant; LOE= lack of efficacy; yoa= years of age; DMARD= disease modifying antirheumatic agent; CCX= corticosteroids; GCX= glucocorticoids; MTX= methotrexate; *= 100mm Visual Analogue Scale, AE= adverse events; RR = risk ratio; 95% CI= 95% confidence interval;

TABLE 3: ETODOLAC FOR RHEUMATOID ARTHRITIS

TRIAL	Jacob 1985 (5)	Lightfoot, 1997 (6)	Neustadt, 1997 (7)
Intervention	etodolac 100-600mg/day	LOW: 200mg/day bid etodolac HIGH: 300mg/day bid etodolac	LOW: 2 x 150mg/day etodolac HIGH: 2 x 500mg/day etodolac
Control	aspirin 3600 -4800mg/day	20mg/day piroxicam	4 x 600mg/day ibuprofen
Country	U.S.	U.S. & Europe	U.S.
No. of patients Total (arms)	475 (239, 236)	426 (140, 147, 139)	1446 (620, 409, 417)
% female Intervention(s) Control	74 71	75, 70 69	71, 69 72
Mean age Intervention(s) Control	49 49	57, 58 56	53.2, 53.0 53.1
Design	51 week, double-blind, randomised, multicentre	12 week, double blind, parallel, randomised, multicentre	3 year, double-blind, randomised, parallel, multicentre

TABLE 4: ETODOLAC FOR OSTEOARTHRITIS

TRIAL	<u>Dick, 1992 (8)</u>	<u>Eisenkolb, 1993 (9)</u>	<u>Grisanti, 1992 (10)</u>	<u>Lucker, 1994 (11)</u>	<u>Paulsen, 1991 (12)</u>
Intervention	2 x 300mg/day	3 x 200mg/day	3 x 200mg/day	2 x 300mg/day	2 x 300mg/day
Control	20mg piroxicam	3 x 50mg diclofenac	3 x 50mg diclofenac	2 x 100mg nimesulide	20mg/day piroxicam
Country	U.K. & Netherlands	Germany, UK and Switzerland	Chile, Portugal & Brazil	Germany & Switzerland	Chile, Argentina, Portugal and Brazil
No. of patients					
Total (arms)	116 (57, 59)	135 (66, 69)	172 (85, 87)	199 (99, 100)	220 (112, 108)
% female					
Intervention(s)	72	65	86	65	78
Control	64	65	86	68	77
Mean age					
Intervention(s)	59.5	61.4	59	63.7	58.0
Control	57.3	60.5	59	65.0	58.0
Design	6 week, double-blind, randomised, multicentre	6 week, double-blind, randomised, multicentre	8 week, double-blind, randomised, multicentre	12 week, double-blind, randomised, multicentre	8 week, double-blind, randomised, multicentre

TABLE 4 (CONT'D): ETODOLAC FOR OSTEOARTHRITIS

TRIAL	Perpignano, 1994 (13)	Rogind, 1997 (14)	<u>Schnitzer, 1995 (15)</u>	<u>Williams, 1989 (16)</u>
Intervention	600mg/day etodolac SR	600mg/day etodolac	2 x 400mg/day	2 x 300mg/day
Control	20mg/day tenoxicam	20mg/day piroxicam	1500mg/day nabumetone placebo	placebo
Country	Italy	Denmark	U.S.	U.K.
No. of patients Total (arms)	120 (60, 60)	271 (138, 133)	270 (91, 89, 90)	210 (104, 106)
% female Intervention(s) Control	85.0 91.7	79.7 77.4	70.3 69.7, 65.6	55.8 54.7
Mean age Intervention(s) Control	70.4 71.0	67.0 67.5	63.8 62.4, 65.3	62.1 63.3
Design	8 week, double-blind, double-dummy, randomised, multicentre	8 week, double-blind, double-dummy, randomised, multicentre	4 week, double-blind, randomised, multicentre	4 week, double-blind, randomised, multicentre

TABLE 5: MELOXICAM FOR OSTEOARTHRITIS

TRIAL	Dequeker, 1998 (SELECT) (17)	Goei The, 1997 (18)	Hawkey, 1998 (MELISSA) (19)	<u>Hettich, 1997 (20)</u>	Hosie, 1996 (21)
Intervention	7.5mg/day meloxicam	15mg/day meloxicam	7.5mg/day meloxicam	15mg/day meloxicam	7.5mg/day meloxicam
Control	20mg/day piroxicam	100mg/day diclofenac SR	100mg/day diclofenac SR	100mg diclofenac retard	100mg/day diclofenac SR
Country	Various	Various	Various	Germany	U.K.
No. of patients Total (arms)	8656 (4320, 4336)	258 (128, 130)	9323 (4635, 4688)	253	335 (169, 166)
% female Intervention(s) Control	68 67	85.2 82.3	66.8 67.1	not stated	59.2 59.0
Mean age Intervention(s) Control	61.3 61.6	71.5 71.4	61.5 61.7	not stated	64.3 64.2
Design	4 week, double-blind, double-dummy, randomised, multicentre	6 week, double-blind, randomised, multicentre	4 week, double-blind, double-dummy, randomised, multicentre	12 week, double-blind, randomised, parallel	6 month, double-blind, randomised, multicentre

TABLE 5 (CONT'D): MELOXICAM FOR OSTEOARTHRITIS

TRIAL	Hosie, 1997 (22)	Hsu, 1999 (23)	Linden, 1996 (24;25)	Yocum, 1999 (26)
Intervention	15mg/day meloxicam	7.5mg/day meloxicam	15mg/day meloxicam	7.5mg or 15mg/day meloxicam
Control	20mg/day piroxicam	100mg diclofenac retard	20mg/day piroxicam	2 x 50mg diclofenac or placebo
Country	U.K.	Taiwan	various	U.S.
No. of patients				
Total (arms)	455 (306, 149)	282 (140,142)	256 (129, 127)	774 (154,154,156,153,157)
% female				
Intervention(s)	58.2	not stated	62.8	63.6
Control	53.7		63.0	68.0, 65.0
Mean age				
Intervention(s)	65.5	not stated	67.2	not stated
Control	64.0		67.2	
Design	Six month, double-blind, randomised, multicentre	4 week, double-blind, randomised, parallel, double-dummy	6 week, double-blind, randomised, multicentre	12 week, double-blind, randomised, double-dummy, parallel, multicentre

TABLE 6: ROFECOXIB FOR RHEUMATOID ARTHRITIS

TRIAL	Bombardier, 2000 (VIGOR) (27)	Schnitzer, 1999 (28)
Intervention	50mg/day rofecoxib	5 or 25 or 50mg/day rofecoxib
Control	2 x 500mg/day naproxen	Placebo
Country	Various	U.S.
No. of patients Total	8076	658
% female Total	79.7	76.9
Mean age Intervention(s) Control	58 58.2	54.8, 55.7, 54.4 54.7
Design	0.5 – 13 month, double-blind, randomised, multicentre	8 week, double-blind, randomised, multicentre

TABLE 7: ROFECOXIB FOR OSTEOARTHRITIS

TRIAL	<u>Acevedo, 1999 (29;30)</u>	<u>Cannon, 2000 (31;32)</u>	<u>Day, 2000 (33;34)</u>	<u>Ehrich, 1997 (35-38)</u>	<u>Ehrich, 1999 (39)</u>	<u>Geba, 1999 (40)</u>	<u>Geba, 2000 (41)</u>	<u>Hawkey, 2000 (42)</u>
Intervention	12.5 or 25mg/day rofecoxib	12.5 or 25mg/day rofecoxib	12.5 or 25mg/day rofecoxib	5 or 12.5 or 25 or 50mg/day rofecoxib	25 or 125mg/day rofecoxib	12.5mg/day rofecoxib	12.5 or 25 mg/day rofecoxib	25 or 50mg/day rofecoxib
Control	3 x 50mg/day diclofenac	3 x 50mg/day diclofenac	3 x 800mg/day ibuprofen or placebo	placebo	placebo	1000mg/day nabumetone or placebo	200mg celecoxib 4 x 1g paracetamol	3 x 800mg/day ibuprofen or placebo
Country	various	U.S.	various	U.S.	U.S.	U.S.	U.S.	various
No. of patients Total	693	784	809	672	219	1042	382	775
% female Total	not stated	67.5	80.9	71	71.2	not stated	68.3	74.5
Mean age Intervention(s) Control	not stated	62.8, 62.8 62.5	64.9, 62.8 64.1, 63.1	(total) 61.7	64.0, 63.9 62.6	(total) 63	63.4, 61.3 62.6, 63.1	62, 61 61, 62
Design	One year, double-blind, randomised, multicentre	One year, double-blind, randomised, multicentre	6 week double-blind, randomised, multicentre	6 week double-blind, randomised, multicentre	6 week double-blind, randomised, multicentre	6 week, double-blind, randomised, multicentre	6 week double-blind, randomised, multicentre	24 week blinded, randomised, multicentre

TABLE 7 (CONT'D): ROFECOXIB FOR OSTEOARTHRITIS

TRIAL	<u>Laine, 1999</u> (43;44)	<u>Laurenzi, 2000a</u> (45)	<u>Laurenzi, 2000b</u> (46)	<u>Saag, 1998</u> (30;47)	<u>Truitt, 1999 (48)</u>	<u>Whelton 2000</u> (49)	<u>McKenna 2000</u> (50)
Intervention	25 or 50mg/day rofecoxib	12.5mg rofecoxib	12.5mg rofecoxib	12.5mg or 25mg rofecoxib	12.5 or 25mg/day rofecoxib	25mg rofecoxib/day	25mg rofecoxib/day
Control	3 x 800mg/day ibuprofen or placebo	naproxen 1g/day nabumetone 1g/day	2 x (diclofenac 50mg/misoprostol 200mcg)/day	800mg/day ibuprofen or placebo	1500mg/day nabumetone or placebo	200mg celecoxib/day	200mg celecoxib/day or placebo
Country	U.S.	U.S.	various	various	U.S.	U.S.	U.K. & U.S.
No. of patients Total	742	482	483	736	341	810	182
% female Total	67.5	not stated	80.3	not stated	not stated	not stated	not stated
Mean age Intervention(s) Control	62, 62 62, 61	63 (total)	62.1 (total)	not stated	83(total)	not stated	not stated
Design	6 month, double-blind, randomised	6 week double-blind, randomised multicentre	6 week double-blind, randomised multicentre	6 week double-blind, randomised, multicentre	6 week double-blind, randomised, multicentre	6 week double-blind, randomised, multicentre	6 week double-blind, randomised, multicentre

TABLE 8: CELECOXIB FOR RHEUMATOID ARTHRITIS

TRIAL	Simon, 1998 (51), Searle 012 (52)	<u>Searle 023 (53): DATA SUBMITTED COMMERCIAL IN CONFIDENCE</u>	Simon, 1999(54), Geis, 1998 (55), Zhao, 2000 (56), Searle 022 (57)	Emery, 1999 (58); Geis, (59), Searle 041 (60)
Intervention	2 x 40mg or 2 x 200mg or 2 x 400mg/day		2 x 100mg or 2 x 200mg or 2 x 400mg/day	2 x 200mg/day
Control	Placebo		2 x 500mg naproxen or placebo	2 x 75mg diclofenac SR
Country	U.S.		U.S. & Canada	Various
No. of patients Total (arms)	330 (81, 82, 82, 85)		1149 (240, 235, 218, 225, 231)	655 (326, 329)
% female Intervention(s) Control	67, 89, 79 75		74, 73, 72 72, 73	76 71
Mean age Intervention(s) Control	55.6, 55.5, 56.7 56.5		54, 55, 54 55, 54	55.9 54.5
Design	4 week double-blind randomised multicentre		12 week, double-blind, randomised, multicentre, placebo controlled	24 week, double-blind, double- dummy, randomised, parallel, multicentre

TABLE 9: CELECOXIB FOR OSTEOARTHRITIS

TRIAL	Williams, 2000 (61) Zhao,1999 (62), Geis, 1999 (63), Searle 060 (64)	Searle 047 (65): DATA SUBMITTED COMMERCIAL IN CONFIDENCE	Geis, 1999 (63) Searle 087 (66)
Intervention	1 x 200mg or 2 x 100mg/day		1 x 200mg or 2 x 100mg/day
Control	Placebo		Placebo
Country	U.S.		U.S.
No. of patients Total (arms)	686 (231, 223, 232)		718 (243, 231, 244)
% female Intervention(s) Control	67, 66 67		69, 69 73
Mean age Intervention(s) Control	63.0, 62.7 62.6		62.0, 61.3 61.3
Design	6 week double-blind, randomised, multicentre		6 week, double-blind, randomised, Multicentre trial

TABLE 9 (CONT'D): CELECOXIB FOR OSTEOARTHRITIS

TRIAL	Bensen, 1999 (67), Zhao, 1999 (68) Hubbard, 1998 (69) 1999 (70), Zhao (71), Searle 020 (72)	<u>Searle 021(73) : DATA SUBMITTED COMMERCIAL IN CONFIDENCE</u>	Geis, 1999 (74), Zhao (71), Searle 054 (75)	<u>Searle 118 (75)</u>	<u>Searle 042(76)</u>
Intervention	2 x 50mg/day or 2 x 100mg/day or 2 x 200mg/day		2 x 50 or 100 or 200mg/day	2 x 100mg/day	2 x 100mg/day
Control	2 x 500mg/day naproxen or placebo		2 x 500mg/day naproxen placebo	3 x 50mg diclofenac/day placebo	2 x 50mg diclofenac
Country	U.S. & Canada		U.S. & Canada	U.S.	Various
No. of patients Total (arms)	1004 (203, 197, 202, 198, 204)		1061 (216, 207, 213, 207, 218)	600 (201, 199, 200)	688 (347, 341)
% female					
Intervention(s)	69, 73, 72		65, 65, 67	68, 62	71
Control	71, 75		66, 67	66	72
Mean age					
Intervention(s)	62, 62, 63		62.3, 61.9, 61.4	61.9, 62.7	63.2
Control	62, 62		63.5, 63.6	60.4	64.1
Design	12 week double-blind, randomised, multicentre, parallel		12 weeks double-blind, randomised, multicentre	6 week, double-blind, randomised, multicentre trial	6 week, double-blind, double-dummy, randomised, multicentre trial

TABLE 10: CELECOXIB FOR RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS

TRIAL	Silverstein, 2000 (77) Searle 102 CLASS study	Burr, 1999 (78) Searle 062 (79)	Searle 071 (80): DATA SUBMITTED COMMERCIAL IN CONFIDENCE
Intervention	2 x 400mg/day	2 x 200mg/day	
Control	3 x 800mg ibuprofen or 2 x 75mg/day diclofenac	2 x 500mg/day naproxen	
Country	U.S. & Canada	U.S.	
No. of patients Total (arms)	7968 (3987, 1985, 1996)	537 (270, 267)	
% female Intervention(s) Control	68.5 69.1	67 67	
Mean age Intervention(s) Control	60.6 59.8	56.7 57.7	
Design	26-52 weeks, double-blind, randomised, multicentre	12 week, double-blind, randomised, controlled, multicentre	

TABLE 11: ETODOLAC VS. PLACEBO FOR OSTEOARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Williams, 1989 (16) Etodolac 300mg/bd Placebo N=210, 4 weeks, OA of hip or knee >18-75 yoa concomitant therapy not permitted</p>	<p>Joint tenderness on pressure (1-5) Joint swelling(1-5) Knee flexion or hip mobility Patient and investigator overall condition(1-5) Weight bearing pain on activity(1-5) Pain intensity(1-5) Weight bearing pain scores (1-5)</p>	<p>EFFICACY: Significantly greater improvement at week 1 and 4 was seen for weight bearing pain, joint swelling and overall assessments in knee and for weight bearing pain, joint tenderness and overall assessments for hip p<0.05.</p> <p>SAFETY: Trend favouring placebo all outcomes, but no difference statistically significant. Rate of withdrawals due to AE RR = 1.22 (95% CI: 0.39, 3.88) , or due to GI symptoms RR=1.02 (95% CI: 0.26, 3.97)]. Total AE RR=1.47 (95% CI: 0.86, 2.52), GI AE RR=1.53 (95% CI: 0.78, 3.01). Similar incidence of AEs in over and under 65s. RR=1.45 (95% CI: 0.66, 3.19) and RR=1.54 (95% CI: 0.74, 3.23) respectively.</p>
<p>Schnitzer 1995 (15)</p>	<p>see etodolac vs. NSAID table</p>	<p>see etodolac vs. NSAID table</p>

TABLE 12: ETODOLAC VS. NSAIDS FOR OSTEOARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Dick, 1992(8) Etodolac 300mg/bd Piroxicam 20mg/day N=116, 6 weeks, OA of knee Confirmed by x-ray findings 18-75 yoa paracetamol rescue ? concomitant therapy</p>	<p>Patient and investigator global assessments (1-5) Night pain (1-5) Spontaneous pain intensity(1-5) Pain on standing, walking, getting in/out of bed, up from a chair and climbing stairs (1-5) Tenderness on pressure(1-5) Degree of swelling(1-5) Crepitus and degree of erythema(1-5) Knee flexion Duration of morning stiffness</p>	<p>EFFICACY: Mean scores for 13 of 15 efficacy measurements were significantly improved from baseline for both groups, but there were no significant differences between groups. Improvements evident after 2 weeks of therapy and maintained through 6 weeks. Trend suggesting superiority of etodolac but not SS.</p> <p>SAFETY: No significant differences between groups in AE profile, but trend favouring piroxicam: AE withdrawals RR=2.48 (95% CI: 0.93, 6.60), GI withdrawals RR = 2.33 (95% CI: 0.76, 7.14), AE total RR=1.22 (95% CI: 0.79, 1.89).</p>
<p>Eisenkolb, 1993 (9) Etodolac 200mg/td Diclofenac 50mg/td N=135, 6 weeks, OA of knee Confirmed by x-ray findings 18-75 yoa previous NSAID therapy</p>	<p>Patient and investigator global assessments(1-5) Night pain(1-5) Spontaneous pain intensity(1-5) Pain on standing, walking, getting in/out of bed, up from a chair and climbing stairs(1-5) Tenderness on pressure(1-5) Degree of swelling(1-5) Crepitus and degree of erythema Knee flexion Duration of morning stiffness</p>	<p>EFFICACY: Baseline arthritic symptoms were worse for the Etodolac group than diclofenac group. Efficacy scores were similar for the two therapy groups, with no significant differences between groups for any assessment. Improvement in patients' global assessment from baseline was seen in 50% of etodolac patients and 40% of diclofenac. Improvement in investigators' global assessment from baseline was seen in 42% of etodolac patients and 34% of diclofenac.</p> <p>SAFETY: No significant differences between groups in AE profile. AE withdrawals RR=0.93 (95% CI: 0.38, 2.26), GI withdrawals RR = 1.74 (95% CI: 0.43, 7.00).</p>
<p>Grisanti, 1992 (10) Etodolac 200mg/td Diclofenac 50mg/td N=172, 8 weeks, OA of knee Confirmed by x-ray previous NSAID therapy with demonstrated flare ? concomitant therapy</p>	<p>Patient/ physician rating of overall condition(1-5) Pain intensity (1-5) Night pain (1-5) Pain on standing, walking, getting in/out of bed, up from a chair and climbing stairs(1-5) Tenderness on pressure (1-5) Degree of swelling (1-5), erythema (1-5) Duration of morning stiffness Walking time</p>	<p>EFFICACY: No significant differences between groups. Significant improvement in the patients' overall condition was seen in both groups, by the second week of treatment, and continued throughout the study. All efficacy assessments showed ss improvements from baseline for both groups, at final assessment.</p> <p>SAFETY: No significant differences between groups in AE profile, but trend favouring etodolac: AE withdrawals RR=0.26 (95% CI: 0.03, 2.24), GI withdrawals RR = 0.26 (95% CI: 0.03, 2.24), AE total RR=0.83 (95% CI: 0.47, 1.46).</p>

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Lucker, 1994 (11) Etodolac 300mg/bd Nimesulide 100mg/bd N=199, 12 weeks, OA of knee 30-80 yoa minimum one year duration painful exacerbation at least 15 days duration excluded if very severe disease no concomitant CCX. 80% power to detect 20% difference in therapeutic efficacy at 5% significance with sample size of 200 allowing for 15% dropout rate.</p>	<p>Patient and physician overall condition (0-3) Spontaneous pain * Lequesne index adverse events. compliance</p>	<p>EFFICACY: Pain score highly SS decrease for both groups. No significant differences between treatment groups were noted for any assessment at 12 weeks.</p> <p>SAFETY: No significant differences between groups in AE profile, but trend favouring etodolac except: AE withdrawals RR=1.52 (95% CI: 0.56, 4.10), GI AE RR = 0.81 (95% CI: 0.52, 1.27), AE total RR=0.88 (95% CI: 0.61, 1.27)</p>
<p>Paulsen, 1991 (12) Etodolac 300mg/bd Piroxicam 20mg/day N=220, 8 week, OA of knee Radiologically demonstrated previous therapeutic response to NSAID with flare on withdrawal CCX not permitted</p>	<p>Patient and investigator rating of overall condition (1-5) Pain intensity (1-5) Night pain (1-5) Pain on standing, walking, getting in/out of bed, up from a chair and climbing stairs(1-5) Tenderness, swelling, erythema, knee flexion(1-5) Time to walk 50 feet Morning stiffness AEs, withdrawals due to AEs</p>	<p>EFFICACY: SS improvement both groups for all primary assessments from baseline (pain, weight bearing, inflammation and mobility assessments). No significant differences between treatment groups were noted for any assessment.</p> <p>SAFETY: No SS differences between groups: Total AE RR=1.21 (95% CI: 0.66, 2.20), GI AE RR=0.88 (95% CI: 0.41, 1.92), Withdrawals: Total RR=1.12 (95% CI: 0.66, 2.20), GI: RR=1.29 (95% CI: 0.29, 5.61). 1 patient on etodolac withdrew because of GI bleeding.</p>
<p>Perpignano1994 (13) etodolac 600mg/day SR tenoxicam 20mg/day N= 120, 8 weeks, knee and hip Over 65 years of age history of positive response to anti-inflammatory drugs no concomitant CCX</p>	<p>global pain* pain on movement (PAM) (1-5) pain at night (1-5) joint tenderness (1-5) joint motility at flexion Lequesne score patient global overall clinical condition investigator global overall clinical condition AEs, withdrawals due to AEs endoscopy in subgroup of 60 patients</p>	<p>EFFICACY: tenoxicam group higher PAM at baseline. SS improvement both groups all parameters with no SS differences between groups etodolac group only: slight but significant improvements in global clinical condition. Trend suggesting tenoxicam more mobility but more PAM p<0.02.</p> <p>SAFETY: SS fewer AE in etodolac group but GI events fewer but not SS: Total AE RR=0.36 (95% CI: 0.14, 0.93), GI AE RR=0.44 (95% CI: 0.14, 1.37), Withdrawals: Total RR=0.71 (95% CI: 0.24, 2.13).</p> <p>ENDOSCOPY: baseline no differences. In patients presenting with no lesions at baseline 8 in tenoxicam and 1 in etodolac presented lesions OR=8.8 (95% CI: 0.99, 410.6) p<0.031. Cumulative endoscopic index significantly higher in tenoxicam group post therapy p<0.03.</p>

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Rogind, 1997 (14) etodolac 300mg/bd piroxicam 20mg/day N=271, 8 weeks, hip and knee Over 40 years of age No concomitant DMARDs or CCX paracetamol rescue 80% power to detect difference with respect to GI AEs (assuming 0.10 and 0.25 frequency) at 5% level if 250 patients included assuming 20% dropout.</p>	<p>Range of motion (goniometer) Contraction Joint swelling tenderness (1-5) Crepitus (yes/no) investigator overall clinical assessment (1-5) patient: weight bearing pain (1-5) patient: pain at rest (1-5) Duration of joint stiffness (minutes) patient overall clinical assessment (1-5)</p> <p>NB all change in all variables from baseline to end of treatment analysed using 3 point scale improved/no change/worse.</p>	<p>EFFICACY: Both groups SS improvement in all primary assessments at 4 and 8 weeks. No SS differences between groups in any variable. In both groups for each outcome approximately 50% patients experience no change/worse.</p> <p>SAFETY: SS fewer AE in etodolac group but GI events fewer but not SS: Total AE RR=0.63 (95% CI: 0.45, 0.87), GI AE RR=0.68 (95% CI: 0.44, 1.05), Withdrawals: Total RR=0.72 (95% CI: 0.41, 1.27), GI: RR=0.66 (95% CI: 0.34, 1.28). 3 patients on piroxicam reported PUB.</p>
<p>Schnitzer, 1995 (15) Etodolac 400mg/bd (supratherapeutic dose) Nabumetone 1500mg/day or placebo N=270, 4 weeks, OA of knee Radiologically confirmed >40 yoa treatment with aspirin or other NSAID within previous 3 months concomitant CCX or cytoprotective agents not permitted but concomitant low dose aspirin permitted.</p>	<p>Patient and investigator rating overall condition(1-5) Joint tenderness on palpation (0-4) Walking pain(0-4) Night-time pain(0-4) Quality of sleep Severity of inactivity stiffness(0-4) Adverse events</p>	<p>EFFICACY: SS improvement in all efficacy assessments relative to baseline at all visits in two NSAID groups (P<0.001) and also in placebo at most visits (P<0.05). By week 4 improvements in global assessments were significantly greater in the study groups p<0.05. Improvements investigator and patient global assessments greater in etodolac than nabumetone p=0.009.</p> <p>SAFETY: No difference between treatment groups in all arms (including placebo). Etodolac vs. nabumetone: Total AE RR=1.27 (95% CI: 0.77, 2.11), AE withdrawals RR=0.78 (95% CI: 0.32, 1.89). Hypokalaemia in three patients nabumetone (p=0.035). Equivalent rates of GI events over 3% patients in active treatment groups not placebo but not reported in detail.</p>

TABLE 13: ETODOLAC VS. NSAID FOR RHEUMATOID ARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Jacob 1985 (5) titrated doses of etodolac between 100-600mg/day titrated levels of aspirin to 3600-4800mg/day N=475, 51 weeks history of positive therapeutic response functional class/progression stage I to III paracetamol rescue concomitant therapy including DMARDs permitted</p>	<p># painful joints # swollen joints morning stiffness (hrs) grip strength (mmHg) 50 ft walking time (secs) investigator global clinical patient self assessment pain intensity articular index (#painful/swollen joints) ESR</p>	<p>EFFICACY: data questionable: first four weeks not equivalent in terms of therapeutic doses as in titration period. Twice as many patients withdrew due to lack of efficacy in etodolac group during first four weeks but no patient numbers given for efficacy results. SS improvement both groups each time point (p<0.05) all OMs with no SS differences between groups.</p> <p>SAFETY: Etodolac patients fewer withdrawals due to AE [RR=0.39 (95% CI: 0.27, 0.58)]. Etodolac patients significantly less nausea, vomiting and abdominal pain p<0.05.</p>
<p>Lightfoot 1997 (6) etodolac 200mg <i>bd</i> etodolac 300mg <i>bd</i> piroxicam 20mg <i>qid</i> N=426, 12 week 18 to 75 yoa previous positive response to NSAIDs ARA diagnostic criteria at least 6 months disease duration no concomitant NSAIDs paracetamol rescue CCX and DMARDs permitted</p>	<p>investigator and patient Global assessments (1-5) # painful joints (/69) # swollen joints(/66) pain intensity (1-5) painful joint score (0-3) swollen joint score(0-3) articular index grip strength (mmHg) ESR duration morning stiffness(min) time to walk 50 ft(sec) AEs, withdrawals due to AEs</p>	<p>EFFICACY: all 3 groups significant improvement in primary outcomes at 12 weeks. E300 equivalent to piroxicam in all cases. E200 significantly less improvement than other groups week 4 patient global assessment.</p> <p>SAFETY: No difference between groups in rate of withdrawals due to AE 400mg [RR= 0.60 (95% CI: 0.22, 1.59)], 600mg : [RR=0.66 (95% CI: 0.26, 1.69)] or due to GI symptoms 400mg [RR=0.55 (95% CI: 0.19, 1.60)] 600mg [RR=0.76 (95% CI: 0.28, 1.92)] . No differences in rate of any specific event. No patients in etodolac group, 3 in piroxicam ulcers after endoscopy due to symptoms.</p>

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Neustadt 1997 (7) etodolac 300mg/day (subtherapeutic dose) etodolac 1000mg/day (supratherapeutic dose) ibuprofen 2400mg/day N= 1446, up to 3 years early stage RA ARA DMARDs not permitted low dose prednisolone <5mg/day permitted premature discontinuation of study with only 20% completing the three years unlicensed doses</p>	<p>investigator and patient global assessment (1-5) # painful joints # swollen joints ACR remission of RA (duration of morning stiffness, fatigue, joint pain by history, joint tenderness or pain in motion, soft tissue swelling in joints or tendon sheaths, ESR) morning stiffness grip strength time to walk 50 ft articular index time to onset of fatigue joint pain by history Steinbrock's disease stage ACR functional class ESR, RF and CRP</p>	<p>EFFICACY: first 2 months: low and high dose etodolac equivalent to ibuprofen with later trend suggesting etodolac superior; etodolac SS> ibuprofen #swollen joints from 14 weeks; high dose etodolac SS to ibuprofen patients global. Similarly both etodolac doctors global although not SS at all visits. Neither drug altered disease progression. No other SS differences between patient groups. Subgroup analysis no difference sex, age, type RA onset, family history, duration of RA ,#swollen joints, duration morning stiffness.</p> <p>SAFETY: AE withdrawals equivalent all groups. SS less dyspepsia in etodolac 300 mg group. PUBs: 2 in each of etodolac group, 9 in ibuprofen p=0.005. RR= 0.23 (95% CI: 0.05, 1.04).</p>

TABLE 14: MELOXICAM VS. PLACEBO FOR OSTEOARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Yocum 1999 (26) meloxicam 7.5mg or 15mg /day placebo N=467, 12 weeks, hip and knee ≥40 yoa demonstrated flare following NSAID withdrawal rescue medication permitted</p>	<p>WOMAC total patient pain* patient* and investigator (1-5) global disease activity pain on movement* pain at rest* global efficacy (1-4) LOE withdrawals change in arthritic condition incidence and intensity of AEs withdrawals due to AEs</p>	<p>EFFICACY: meloxicam 7.5 mg, 15mg and diclofenac treated patients showed a SS improvement from baseline ($p < 0.001$) that was SS superior to placebo in all outcomes. Dose response observed WOMAC.</p> <p>SAFETY: GI- AE for meloxicam comparable $p = 0.95$, no SS difference between treatments in withdrawal due to AE. No dose response observed. The following relative risks were observed for 7.5mg and 15mg respectively: Total AE: 1.17 (95% CI: 0.94, 1.45); 1.21 (95% CI: 0.98, 1.49). Total GI AE: 1.17 (95% CI: 0.73, 1.86), 1.01 (95% CI: 0.62, 1.63). Total AE withdrawals 1.87 (95% CI: 0.71, 4.93), 2.18 (95% CI: 0.85, 5.59). GI withdrawals 2.55 (95% CI: 0.50, 12.94), 3.02 (95% CI: 0.62, 14.73).</p>

TABLE 15: MELOXICAM VS. NSAIDS FOR OSTEOARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Dequeker 1998 (17) meloxicam 7.5mg/day piroxicam 20mg/day N=9286, 4 weeks, hip, knee, hand or vertebral spine ≥18 yoa ? concomitant DMARDs permitted</p>	<p>pain on movement* pain at rest* investigator and patient global efficacy (1-4) patient change in condition (1-4) patient overall condition (1-3) investigator overall change (1-3) global efficacy (1-3) LOE patient and investigator global tolerance (1-4) incidence AEs, withdrawals due to AEs, GI AEs</p>	<p>EFFICACY: no significant differences between comparators in any of parameters measured.</p> <p>SAFETY: good/satisfactory in 90% Meloxicam and 88% piroxicam. Meloxicam fewer AE [RR 0.80 (95% CI: 0.75, 0.87)] , GI AE [RR 0.67 (95% CI: 0.60, 0.75)] , (p<0.001), withdrawals due to GI AE [RR 0.72 (95% CI: 0.59, 0.88)] (p<0.01) and withdrawals due to AE [RR 0.85 (95% CI: 0.72, 0.99)] . Patients previously treated for peptic disease higher incidence of GI AEs, but lower in meloxicam group [RR 0.81 (95% CI: 0.60,1.10)]. PUBs 7 patients with meloxicam, 16 piroxicam [RR 0.44 (95% (95% CI: 0.18, 1.07)]. No difference in rate of serious AEs. Hospitalisations for GI AEs occurred in 6 meloxicam patients and 7 piroxicam for at total of 56 versus 121 days respectively.</p>
<p>Goei Thè 1997(18) meloxicam 15mg/day diclofenac 100mg/day N=258, 6 weeks, knee ≥18 yoa confirmed diagnosis no concomitant therapy paracetamol rescue</p>	<p>pain on movement patient global efficacy* 24h worst pain at rest* Lequesne index of severity paracetamol consumption LOE withdrawals</p> <p>tolerance since last visit* global tolerance* AEs, GI AEs, AE withdrawals</p>	<p>EFFICACY: trend in favour of meloxicam in pain on movement, pain at rest, global efficacy, total severity index and paracetamol consumption but not SS.</p> <p>SAFETY: equivalent total AEs (RR= 0.95 (95% CI: 0.68, 1.32) and AE withdrawals (RR=0.89 (95% CI: 0.52, 1.51). Diclofenac increased rate GI ADRs: RR 0.63 (95% CI: 0.39, 1.02). One patient in diclofenac group developed gastric ulcer.</p>

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Hawkey 1998 (19) meloxicam 7.5mg/day diclofenac 100mg/day N=9323, 4 weeks, hip, knee, hand or vertebral spine ≥18 yoa ? concomitant DMARDs permitted Study >80% powered to detect a difference of ~1% difference in incidence of AEs occurring at rate of at least 2%</p>	<p>pain on movement* pain at rest* investigator and patient global efficacy (1-4) patient change in condition (1-3) patient overall condition (1-4) investigator overall change: (1-3) LOE patient and investigator global tolerance (1-4) AEs, GI AEs, AE withdrawals, PUB, global tolerance</p>	<p>EFFICACY: both treatments produced SS improvement in disease with no SS differences. Suggested superiority of diclofenac although small difference 4.5-9% difference which was within range of therapeutic equivalence. LOE withdrawals: OR 1.66 (1.16 to 2.38) in favour of diclofenac. Fewer patients withdrawing due to LOE or AEs in meloxicam group p=0.0014.</p> <p>SAFETY: good/satisfactory in 90% meloxicam and 87% diclofenac (p=0.001). Fewer patients reporting AEs on meloxicam than diclofenac p<0.001, GI AEs p<0.001, withdrawals due to AEs p<0.001. Rates in >65 yoa 13% vs. 19%, <65 yoa 12% vs. 16%. PUB: 5 meloxicam, 7 diclofenac. 3 patients hospitalised for 5 days on meloxicam vs. 10 patients, 121 days diclofenac, including 4 patients, 31 days in intensive care.</p>
<p>Hettich 1997 (20) meloxicam 15mg/day diclofenac 100mg retard N=253, 12 weeks, hip</p>	<p>worst pain on movement in 24h* worst pain at rest 24h* arthritic condition global efficacy* QOL: multiple causes disability index Global tolerability</p>	<p>EFFICACY: SS improvement in all outcome measures both groups no statistically significant differences between groups QOL: reduction in pain and alleviation and disability associated with significant improvement in QoL (both groups p<0.001). SAFETY: meloxicam favourable GI tolerability (no data) reduced incidence of severe adverse events in meloxicam group 33 vs 14 (p=0.018).</p>
<p>Hosie 1996 (21) meloxicam 7.5mg/day diclofenac 100mg/day SR N=336, 26 weeks, hip and knee ≥18 yoa no concomitant therapy paracetamol rescue</p>	<p>overall pain 7 days * pain on movement * duration of stiffness global efficacy * paracetamol consumption QOL: NHP selected sections global tolerance * AEs, GI AEs</p>	<p>EFFICACY: Improvements in both groups in all parameters but no SS differences.</p> <p>SAFETY: No significant difference in global tolerance. Meloxicam fewer withdrawals due to AE RR 0.67 (95% CI: 0.40, 1.12) equivalent GI RR 0.97 (95% CI: 0.68, 1.37) and total AEs RR 0.99 (95% CI: 0.83, 1.18). Diclofenac one case of melaena.</p>

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Hosie 1997 (22) meloxicam 15mg/day piroxicam 20mg/day N=455, 26 weeks, hip and knee ≥18 yoa ? concomitant DMARDs permitted paracetamol rescue moderate pain in target joint randomised 2:1 80% powered to detect 14% change in overall pain at 5% level with 200 patients enrolled</p>	<p>overall pain* global efficacy* pain on movement* duration of stiffness LOE withdrawals concomitant paracetamol QOL: NHP global tolerability* incidence AEs, withdrawals due to AEs, GI AEs compliance</p>	<p>EFFICACY: no SS difference at 12 weeks but at 6 months meloxicam group SS less overall pain on graph. But validity of using VAS after 6 months questionable and only approx 50% of patients remained with last values carried forward. Graph also shows visit number and not time interval and is misleading.</p> <p>QOL: no SS difference any subscale; physical mobility, energy level, social isolation and influences.</p> <p>SAFETY: no SS differences any parameter but meloxicam lower mean scores and number events. 1 GI bleed in meloxicam group. Withdrawals: all AE RR = 0.78 (95% CI: 0.51, 1.20), GI AE RR = 0.61 [(95% CI: 0.35, 1.06). Total AE RR=0.86 (95% CI: 0.69, 1.07), GI AE RR=0.80(95% CI: 0.58, 1.10).</p>
<p>Hsu 1999 (23) meloxicam 7.5mg/day diclofenac 100mg retard N=282, 4 weeks</p>	<p>global efficacy pain on movement pain at rest change of arthritis condition LOE withdrawals AE: intensity, incidence, withdrawals, causal relationship</p>	<p>EFFICACY: no SS difference between groups any outcome.</p> <p>SAFETY: Significantly fewer GI AEs reported in meloxicam group RR=0.74 (95% CI: 0.57, 0.95), discontinuation due to AEs RR= 0.30 (95% CI: 0.11, 0.79).</p>
<p>Linden 1996 (24;25) meloxicam 15mg/day piroxicam 20mg/day N=255, 6 weeks, hip ≥18 yoa paracetamol rescue 90% powered to detect 15% change in worst pain in target hip on movement last 24 hrs at 5% level with 160 patients enrolled</p>	<p>worst pain on movement in 24h* worst pain at rest 24h+* global efficacy* LOE withdrawals paracetamol consumption Lequesne index of severity incidence AEs, withdrawals due to AEs, GI AEs patient and investigator tolerance* at each visit global tolerance *</p>	<p>EFFICACY: continual SS pain reduction in pain over trial period in both groups with a trend in favour of meloxicam but no SS difference between therapies in primary outcome measure</p> <p>SAFETY: No difference in tolerance at any visit. Withdrawals: all AE RR = 1.18 (95% CI: 0.53, 2.64). Total AE RR=1.03 (95% CI: 0.75, 1.41), GI AE RR=0.92(95% CI: 0.58, 1.46). End of study global: meloxicam approaching SS favourable (p=0.054) in explanatory analysis but not in ITT. 1 perforation in meloxicam group, 3 in piroxicam.</p>

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Yocum 1999 (26) meloxicam: 7.5mg or 15mg/day diclofenac: 2 x 50mg/day N=463, 12 weeks, hip and knee no inclusion/exclusion criteria stated</p>	<p>WOMAC total patient pain* patient* and investigator (1-5) global disease activity pain on movement* pain at rest* global efficacy (1-4) LOE withdrawals change in arthritic condition incidence and intensity of AEs withdrawals due to AEs</p>	<p>EFFICACY: no significant differences but trend suggesting diclofenac superior some outcomes.</p> <p>SAFETY: reduced rate of GI events compared to diclofenac (p=0.02). No PUBs occurred in any group. 7.5mg : Withdrawals: all AE RR =0.84 (95% CI: 0.39, 1.82), GI AE RR = 0.71 [(95% CI: 0.23, 2.19). Total AE RR=0.85 (95% CI: 0.71, 1.01), GI AE RR=0.72(95% CI: 0.48, 1.07). 15mg : Withdrawals: all AE RR =0.98 (95% CI: 0.47, 2.05), GI AE RR = 0.84 [(95% CI: 0.29, 2.44). Total AE RR=0.87 (95% CI: 0.73, 1.04), GI AE RR=0.62(95% CI: 0.40, 0.94).</p>

TABLE 16: ROFECOXIB VS. PLACEBO FOR RHEUMATOID ARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Schnitzer, 1999 (28) rofecoxib 5 or 25 or 50mg/day placebo N=658, 8 weeks >18 yoa history of therapeutic benefit from NSAIDs and to have used therapeutic NSAIDs for ≥ 25 of last 30dys preceding study entry DMARDs permitted oral CCX or MTX but not both but stratified for MTX no SS differences at baseline paracetamol rescue</p>	<p># patients in each group meeting ACR 20 response # tender joints /68 #swollen joints/66 patient global assessment of disease activity* investigator global assessment of disease activity (0-4) patient global pain * CRP</p> <p>QOL: Stanford Health Assessment Questionnaire Disability Index (0-3)</p>	<p>5mg not SS different from placebo. 25mg, 50mg #patients with ARC 20 > placebo (p=0.025, 0.001). Also with patient mean change pain, patient global assessment of disease activity, investigator global assessment of disease activity, SHAQ DI and paracetamol use (p<0.001). Clear separation between 5mg/placebo and higher doses. rofecoxib similar efficacy in patients taking MTX compared to those not</p> <p>QOL: 25mg, 50mg #patients with SHAQ DI (p<0.001). ADRs: only reported those which >3% patient experienced. No SS differences between groups, except greater incidence of rash in 50mg. No difference between groups in the number discontinuing due to GI (3/171 vs 0/168) SHAQ DI= Stanford Health Assessment Questionnaire Disability Index</p>

TABLE 17: ROFECOXIB VS. NSAID FOR RHEUMATOID ARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Bombardier, 2000 (27) 50mg/day rofecoxib 2 x 500mg/day naproxen N=8076, 0.5 to 13 months (81) ≥ 50 yoa or ≥ 40 yoa plus GCX therapy concomitant DMARDs, MTX and CCX permitted paracetamol rescue PUBs had to be clinically confirmed using endoscopy, surgery or radiography.</p>	<p>Investigator and patient global assessment of disease activity (0-4) LOE withdrawals</p> <p>Modified Health Assessment Questionnaire (0-3)</p>	<p>EFFICACY: No SS differences between comparators LOE: rofecoxib 6.3%, naproxen 6.5% NB: GI event defined as PUB</p> <p>SAFETY:</p> <p>RR GI withdrawals 0.74 (95% CI: 0.64, 0.85) RR Total AE withdrawals 1.02 (95% CI: 0.92, 1.12) RR confirmed upper GI event 0.46 (95% CI: 0.33,0.64) p<0.001. RR complicated confirmed upper GI event 0.43(95% CI: 0.24,0.78) p=0.005. RR complicated upper GI bleeding 0.4(95% CI: 0.2,0.7) p=0.004. RR bleeding beyond duodenum 0.5 (95% CI: 0.2,0.9) p=0.03. RR all bleeding events 0.38 (95% CI: 0.25, 0.57) p<0.001. RR upper GI events in patients with previous GI events 0.4 (95% CI: 0.2, 0.8) RR patients with glucocorticoid therapy at baseline 0.4 (95% CI: 0.2, 0.6) RR patients with no glucocorticoid therapy at baseline 0.7 (95% CI: 0.4, 1.2)</p>

TABLE 18: ROFECOXIB VS. PLACEBO FOR OSTEOARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Day 2000 (33;34) rofecoxib 12.5 or 25mg/day placebo N=560, 6 weeks, knee or hip rescue paracetamol stratified into previous NSAID and previous paracetamol >40 yoa ARA Steinbrocker I-III no aspirin or CCX</p>	<p>WOMAC: Pain on walking, pain, stiffness, disability patient global disease* patient overall response(0-4) investigator overall disease status (0-4) investigator overall response joint tenderness (0-3) paracetamol consumption LOE withdrawals</p>	<p>EFFICACY: rofecoxib SS reduction all OMs and SS superior to placebo. LOE : SS fewer withdrawals in active compared to placebo (p≤ 0.009). Maximum effects within 2 weeks.</p>
<p>Ehrich 1997(35) (36-38) [Protocol 029] rofecoxib 5 or 12.5 or 25 or 50mg/day Placebo N=672, 6 weeks, knee and hip* ≥40 yoa pain in affected joint on majority of days each month characteristic radiographic changes ARC I-III worsening of pain following discontinuation of NSAID therapy * hip patients not randomised to 50mg</p>	<p>WOMAC: pain on walking, stiffness, disability patient global assessment response(0-4) investigator global assessment disease status (0-4) SF-36</p>	<p>EFFICACY: all rofecoxib groups SS superior to placebo (p<0.001) all OMs. Dose response higher doses superior to 5mg ?SS Improvements for all doses rofecoxib SS to placebo in all SF 36 domains except general health. Evidence of dose response : 5mg smaller mean changes than other doses for all endpoints.</p> <p>SAFETY: Incidence of discontinuation due to ADRs equivalent between rofecoxib and placebo- no details.</p>
<p>Ehrich, 1999 (39) 25 or 125mg/day rofecoxib Placebo N=219, 6 week, knee >40 yoa ARA I to III positive NSAID response previous and to be taking NSAIDs prior to entry previous GI excluded paracetamol rescue no data on concomitant</p>	<p>WOMAC pain Patient pain * WOMAC physical function/stiffness investigator and patient global response (0-4) investigator and patient global disease status (0-4) LOE withdrawals</p>	<p>LOE: rofecoxib SS to placebo p<0.001 EFFICACY: all endpoints rofecoxib SS superior to placebo (p<0.001). Although some separation in response curves no SS differences between doses (any endpoint) (p<0.05). improvement occurring at week 1 (SS WOMAC pain) and SS at week 2 other outcomes.</p> <p>SAFETY: similar AE withdrawal rates, 1 PUB in 125mg rofecoxib arm.</p>

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Geba 1999(40) rofecoxib 12.5mg/day placebo N=632, 6 wks, knee no inclusion/exclusion details</p>	<p>patient global response (0-4) WOMAC: pain on walking</p>	<p>EFFICACY: Rofecoxib SS superior in number of patients with good or excellent response at 4 hours (p<0.05), 28hrs (p<0.001), 5 days (p not given) and 2, 4, and 6 wks (p<0.05). Patient Global Response: median time to good or excellent response rofecoxib 52hrs, placebo >124 hrs Pain walking over first 5 days rofecoxib greater improvement (p<0.05).</p>
<p>Hawkey 2000 (42) Rofecoxib 25 mg, 50 mg daily Placebo N=582 24 weeks >50 yoa patients with endoscopic evidence of erosive esophagitis, and UGI ulcer were excluded Paracetamol, non-NSAID pain medication and supplied antacids were permitted.</p>	<p>Endoscopically detected ulcers Global assessment of disease by patients Paracetamol use</p>	<p>12 week cumulative rates of endoscopically detected ulcers in rofecoxib arm were similar to those seen in placebo.</p>
<p>Laine 1999 (43) Rofecoxib 25mg 50 mg daily Placebo N=558, 24 weeks >50 yoa Patients with endoscopic evidence of erosive esophagitis, and UGI ulcer (at baseline endoscopy) were excluded Paracetamol, non-NSAID pain medication and supplied antacids were permitted.</p>	<p>Endoscopically detected ulcers Global assessment of disease by patients (0-4) Paracetamol use</p>	<p>The cumulative incidence of endoscopically detected gastroduodenal ulcers ≥3mm with rofecoxib (both doses) was comparable with placebo at 12 weeks (placebo 9.9%, 25 mg rofecoxib 4.1%, 50 mg rofecoxib 14.7%, p<0.001).</p>
<p>Saag 1998 (30;47) [Protocol 033] rofecoxib 12.5mg or 25mg placebo n=515, 6 weeks, hip and knee patients with increased pain following NSAID withdrawal and patients with moderate symptoms taking paracetamol ARA Steinbrocker I-III no aspirin or CCX rescue paracetamol</p>	<p>WOMAC: Pain on walking, pain, stiffness, disability patient global disease* patient overall response(0-4) investigator overall disease status (0-4) investigator overall response joint tenderness (0-3) paracetamol consumption LOE withdrawals</p>	<p>EFFICACY: rofecoxib (both doses) SS superior to placebo (p<0.001) all OMs. SAFETY: RR GI withdrawals 12.5mg 0.79 (95% CI: .0.16, 3.97), 25mg 1.22 (95% CI:0.26, 5.59),</p>

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Truitt 1999 (48) rofecoxib 12.5 or 25mg/day placebo N=226, 6 wks, knee or hip ≥80 yoa aspirin permitted</p>	<p>patient global disease status* investigator global disease status (0-4) WOMAC</p>	<p>EFFICACY: all OMs rofecoxib SS superior to placebo (p≤0.001).</p>

TABLE 19: ROFECOXIB VS. NSAID FOR OSTEOARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Acevedo 1999 (29)[Protocol 034] (also Saag 2000 (30)) rofecoxib 12.5mg or 25mg/day diclofenac 3 x 50mg/day N=693, 52 weeks, hip and knee increased pain following NSAID withdrawal and patients with moderate symptoms taking paracetamol</p>	<p>WOMAC index: pain when walking*, pain, stiffness, functional ability joint tenderness (0-3) investigator global disease status (0-4) patient global disease status * patient global response to therapy (0-4) investigator global response to therapy(0-4) Rescue paracetamol LOE withdrawals</p>	<p>EFFICACY AND SAFETY: Rofecoxib (both doses) of comparable efficacy and tolerability (including GI events) to diclofenac all endpoints. More patients discontinued due to ADRs in diclofenac group (SS not reported). Patient response to therapy: rofecoxib 12.5mg = -2.18, rofecoxib 25mg = -2.33, diclofenac = -2.39 (no reports of SS)</p> <p>RR GI withdrawals 12.5mg 0.47 (95% CI: 0.22, 1.02), 25mg 0.63 (95% CI:0.31, 1.26).</p>
<p>Cannon 2000 (31;32) [Protocol 035] rofecoxib 12.5 or 25mg/day diclofenac 3 x 50mg/day N=784, 52 weeks, hip and knee >40 yoa Steinbrocker I-III increased pain following NSAID withdrawal and patients with moderate symptoms taking paracetamol stratified depending on whether prior NSAID or paracetamol no aspirin or CCX rescue paracetamol</p>	<p>WOMAC index: pain when walking*, pain, stiffness, functional ability joint tenderness (0-3) investigator global disease status (0-4) patient global disease status * patient global response to therapy (0-4) investigator global response to therapy(0-4) Rescue paracetamol LOE withdrawals</p>	<p>EFFICACY: LOE: no SS difference. SS improvement from baseline all groups, all OMs. No SS effect for location of joint i.e. hip or knee, previous medication, age or sex. All primary: treatment response within 2 weeks and maintained throughout study. Although differences between therapies within a priori defined limits, diclofenac SS superior for patient response to therapy and investigator disease status. SAFETY: No SS differences between comparators GI ADRs</p>
<p>Day 2000 (33;34) rofecoxib 12.5 or 25mg/day ibuprofen 3x 800mg/day N=735, 6 weeks, knee or hip stratified into previous NSAID and previous paracetamol >40 yoa ARA Steinbrocker I-III increased pain following NSAID withdrawal and patients with moderate symptoms taking paracetamol no aspirin or CCX rescue paracetamol</p>	<p>WOMAC: Pain on walking, pain, stiffness, disability patient global disease* patient overall response(0-4) investigator overall disease status (0-4) investigator overall response Joint tenderness (0-3) Paracetamol consumption LOE withdrawals</p>	<p>EFFICACY: All responses SS and no SS differences between groups although some separation evident from graphs. Maximum responses within 2 weeks and sustained Rofecoxib 25mg superior to ibuprofen (p=0.005) for pt response and investigator global disease status. Treatment effects consistent for knee v hip, paracetamol v NSAID.</p>

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Geba 1999(40) rofecoxib 12.5mg/day nabumetone 1000mg/day N=834, 6 wks, knee no inclusion/exclusion details</p>	<p>patient global response (0-4) WOMAC: pain on walking</p>	<p>EFFICACY: Rofecoxib SS superior to nabumetone in number of patients with good or excellent response at 28hrs (p<0.001), 5 days (p not given) and 2,4,and 6 wks (p<0.05). Patient Global Response: median time to good or excellent response rofecoxib 52hrs, nabumetone 100hrs, placebo >124 hrs (p=0.002 rofecoxib vs. nabumetone, p=0.001 nabumetone vs. placebo).</p>
<p>Hawkey 2000 (42) Rofecoxib 25 mg, 50 mg daily Ibuprofen 2400 mg / day N=581 24 weeks >50 yoa patients with endoscopic evidence of erosive esophagitis, and UGI ulcer were excluded Paracetamol, non-NSAID pain medication and supplied antacids were permitted.</p>	<p>Endoscopically detected ulcers Global assessment of disease by patients Paracetamol use</p>	<p>Rofecoxib caused fewer endoscopically detected ulcers than did ibuprofen.</p>
<p>Laine 1999 (43) Rofecoxib 25mg 50 mg daily Ibuprofen 2400 mg/ day N=564, 24 weeks >50 yoa Patients with endoscopic evidence of erosive esophagitis, and UGI ulcer (at baseline endoscopy) were excluded Paracetamol, non-NSAID pain medication and supplied antacids were permitted.</p>	<p>Endoscopically detected ulcers Global assessment of disease by patients (0-4) Paracetamol use</p>	<p>The cumulative incidence of endoscopically detected gastroduodenal ulcers ≥3mm with rofecoxib (both doses) was SS lower than with ibuprofen (placebo 9.9%, 25 mg rofecoxib 4.1%, 50 mg rofecoxib 14.7%, and ibuprofen 27.7% p<0.001). ‘equivalent’ individual GI AEs, GI w/d not reported</p>
<p>Laurenzi 2000b (46) rofecoxib 12.5mg/day diclofenac 50mg/misoprostol 200mg b.d. N=483, 6 weeks ≥40 yoa negative faecal occult blood No CCX, aspirin or PPIs permitted Patients stratified according to previous history of gastroduodenal ulcer or GI bleed paracetamol rescue</p>	<p>self-reported diarrhoea abdominal pain discontinuation due to ADRs incidence of GI patient and investigator global disease</p>	<p>EFFICACY: No difference in efficacy (no further details provided). SAFETY: Rofecoxib fewer GI events (28.9% vs. 48.5 %) p<0.001, fewer episodes of diarrhoea (6.2 % vs. 19.9%) p>0.001.</p>

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
Laurenzi 2000a(45) rofecoxib 12.5mg naproxen 500mg I N=482, 6weeks	patient global response (0-4) WOMAC: pain on walking	EFFICACY: Day2 : equivalent clinical improvement (55.8% rofecoxib vs 56.1% naproxen) with ≥ 10 mm improvement WOMAC walking pain scale. Day 6: 86.3% vs 85.4%.
Saag 1998 (30;47) [Protocol 033] rofecoxib 12.5mg or 25mg/day ibuprofen 800mg tds N=667, 6 weeks, hip and knee patients with increased pain following NSAID withdrawal and patients with moderate symptoms taking paracetamol ARA Steinbrocker I-III no aspirin or CCX rescue paracetamol	WOMAC: Pain on walking, pain, stiffness, disability patient global disease* patient overall response(0-4) investigator overall disease status (0-4) investigator overall response joint tenderness (0-3) paracetamol consumption LOE withdrawals	EFFICACY AND SAFETY: No SS differences between groups (efficacy $p \geq 0.05$, ADRs $p \geq 0.1$ and withdrawals due to ADRs $p \geq 0.1$). RR GI withdrawals 12.5mg 0.72 (95% CI: 0.23, 2.24), 25mg 1.11 (95% CI:0.41, 3.02).
Truitt 1999 (48) rofecoxib 12.5 or 25mg/day nabumetone 1500mg /day N=289, 6 weeks, knee or hip ≥ 80 yoa aspirin permitted	Patient global disease status* Investigator global disease status (0-4) WOMAC	EFFICACY AND SAFETY: Results similar– but no reported results of significance tests in abstract or submission.

TABLE 20: ROFECOXIB VERSUS CELECOXIB

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Geba 2000 (41) rofecoxib 12.5 or 25mg/day celecoxib 200mg /day paracetamol 1g qds N=382, 6 weeks, knee ≥40 yoa ARA functional class I-III NSAID responsive or regular user of paracetamol who experienced exacerbation following withdrawal no CCX permitted</p>	<p>WOMAC: Pain on walking, night pain, pain at rest, morning stiffness, functional disability patient overall response (0-4)</p>	<p>EFFICACY: Rofecoxib 25mg SS superior after 5 days to paracetamol (pain walking, night pain, rest pain, pain, stiffness, functional disability (p <0.05). Rofecoxib 25mg SS superior to celecoxib (night pain, rest pain, pain, stiffness, patient global response, (p <0.05). But equivalent on other outcome measures. Rofecoxib 25mg superior to rofecoxib 12.5mg night pain. Rofecoxib 12.5mg v celecoxib: no SS difference any efficacy endpoint early or 6 weeks.</p> <p>SAFETY: No SS difference in ADRs between groups RR total AE = 1.19 (95% CI: 0.93, 1.53) 12.5mg and 1.00 (95% CI: 0.76, 1.32) and AE withdrawals = 1.77 (95% CI: 0.53, 5.85) 12.5mg and 1.53 (95% CI: 0.45, 5.26). GI events not reported.</p>
<p>McKenna 2000 (50) rofecoxib 25mg/day celecoxib 200mg/day N=182, 6 weeks, OA knee ≥40 yoa Abstract only</p>	<p>WOMAC pain, stiffness and physical functioning, total pain* patient global assessment of arthritis</p>	<p>EFFICACY: both groups equivalent improvement pain, global assessment, WOMAC, which was superior to placebo. SAFETY: RR GI adverse events = 3.05 (95% CI: 1.39, 6.68)</p>
<p>Whelton 2000 (49) rofecoxib 25mg/day celecoxib 200mg/day N=810, 6 weeks, older hypertensive OA patients treated with anti-hypertensive medication ≥65 yoa</p>	<p>oedema changes in systolic blood pressure changes in diastolic blood pressure</p>	<p>SAFETY: incidence of oedema rofecoxib > celecoxib (p=0.014). Nearly 60% more patients with rofecoxib (1.6 fold increase) had increase in systolic blood pressure of ≥20mmHg (p<0.05) observed at week 2. At week 6 change in mean baseline bp +2.6mm rofecoxib and – 0.47mm celecoxib (p=0.007). Diastolic bp increased 2.3% rofecoxib compared to 1.2% celecoxib(p=0.29)</p>

TABLE 21: CELECOXIB VS. PLACEBO FOR OSTEOARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Searle 020 (72) Bensen 1999 (67-70;82) Celecoxib 2x50mg, 2x100mg or 2x200mg/day Placebo N=806, 12 weeks, knee ACR functional class I-III No concomitant therapy >18 yoa Aspirin and paracetamol rescue</p>	<p>Patient and investigator global assessments (1-5) Patient pain* OA Severity Index (0-24) (includes pain, walking distance and ADL) WOMAC OA Index APS patient outcome scores Quality of life (SF-36) Adverse events</p>	<p>EFFICACY: significant improvement in all OMs; 50mg/100mg/200mg bid superior to placebo (p<0.05) for all OMs except patient assessed pain for 50mg; 50mg less SS effective than 100mg but not 200mg in WOMAC; data suggests higher dose celecoxib (100mg/200mg) onset at 2 days cf placebo (p<0.05).</p> <p>SAFETY: all doses well tolerated; significance of differences in AEs not reported. Total GI AE (200/400mg) RR=1.19 (95% CI: 0.86, 1.66) and RR=1.09 (95% CI: 0.77, 1.53) respectively. Withdrawals due to GI AE (200/400mg) RR=2.42 (95% CI: 0.87, 6.76) and RR=1.38 (95% CI: 0.45, 4.29) respectively.</p>
<p>Searle 021 (73) DATA SUBMITTED COMMERCIAL IN CONFIDENCE</p>		
<p>Searle 047(65) DATA SUBMITTED COMMERCIAL IN CONFIDENCE</p>		
<p>Searle 054 (75) Geis 1999 (74) Celecoxib 2x50mg, 2x100mg or 2x200mg/day Placebo N=854, 12 weeks, hip ACR functional capacity I-III >18 yoa</p>	<p>Patient and investigator global assessments Patient pain assessment* OA severity index WOMAC OA Index, APS pain score Quality of life (SF-36) Adverse events</p>	<p>EFFICACY: all doses celecoxib statistically superior to placebo for all primary OMs at all assessments (p<0.05); no SS differences between 100mg and 200mb bid doses.</p> <p>SAFETY: no SS differences in AEs causing withdrawal; significance of differences in AEs not reported. Total GI AE (200/400mg) RR=1.59 (95% CI: 1.11, 2.27) and RR=1.65 (95% CI: 1.16, 2.34) respectively. Withdrawals due to GI AE (200/400mg) RR=1.22 (95% CI: 0.42, 3.58) and RR=1.87 (95% CI: 0.70, 4.96) respectively.</p>

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Searle 060 (64) Williams 2000 (61;62) Celecoxib 2 x 100mg/day or 1 x 200mg/day Placebo N=686, 6 weeks, knee ACR functional class I-III No concomitant therapy Paracetamol rescue Aspirin permitted if continuous</p>	<p>Patient and investigator global assessments (1-5) Steinbrockers functional capacity (1-4) Lequesne OA severity Index Patient arthritis pain* WOMAC OA Index, Quality of life (SF-36) Adverse events</p>	<p>EFFICACY: both celecoxib doses statistically superior to placebo in all OMs; no SS differences between doses; SS difference in withdrawal due to LOE, with 24% placebo withdrawal cf <10% celecoxib.</p> <p>SAFETY: no SS differences in AEs. Total GI AE RR=1.23 (95% CI: 0.84, 1.80). Withdrawals due to GI AE RR=0.40 (95% CI: 0.15, 1.05).</p>
<p>Searle 087 (66) Geiss 1999 (63) Celecoxib 2 x 100mg/day or 1x 200mg/day Placebo N=718, 6 weeks, knee ACR functional capacity I-III Concomitant therapy >18 yoa</p>	<p>Patient and investigator global assessments Patient assessment of pain* OA severity index WOMAC OA index Adverse events</p>	<p>EFFICACY: both celecoxib doses statistically superior to placebo in all OMs; no SS differences between doses; SS difference in withdrawal due to LOE, with 23% placebo withdrawal cf <12% celecoxib.</p> <p>SAFETY: significance of differences in AEs not reported. Total GI AE RR=1.26 (95% CI: 0.87, 1.82). Withdrawals due to GI AE RR=0.51 (95% CI: 0.10, 2.53).</p>
<p>Searle 118 (75) Celecoxib 2x 100mg/day Placebo N=401, 6 weeks, knee ACR functional capacity I-III Concomitant therapy >18 yoa</p>	<p>Patient and investigator global assessments Patient assessments of pain* WOMAC OA index APS pain score OA severity index Adverse events</p>	<p>EFFICACY: celecoxib statistically superior to placebo for all OMs (p<0.001).</p> <p>SAFETY: AEs similar but significance of differences not reported. Total GI AE RR=0.93 (95% CI: 0.61, 1.40).</p>

TABLE 22: CELECOXIB VS. NSAID FOR OSTEOARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Searle 020 (72) Bensen 1999 (67-70) (82) Celecoxib 2x50mg, 2x100mg or 2x200mg/day Naproxen 2 x 500mg/day N=800, 12 weeks, knee ACR functional class I-III No concomitant therapy >18 yoa Aspirin and paracetamol rescue</p>	<p>Patient and investigator global assessments (1-5) Patient pain* OA Severity Index (0-24) (includes pain, walking distance and ADL) WOMAC OA Index APS patient outcome scores Quality of life (SF-36) Adverse events</p>	<p>EFFICACY: significant improvement in all OMs, with maximum response evident within 2 weeks; 100mg/200mg bid equivalent efficacy to naproxen for all OMs at all time points (p>0.05), except OA severity index where 100mg superior to naproxen. Naproxen and higher dose celecoxib superior to 50mg celecoxib patient pain assessments and WOMAC.</p> <p>SAFETY: all doses well tolerated; significance of differences in AEs not reported. Total GI AE (200/400mg) RR=0.84 (95% CI: 0.62, 1.12) and RR=0.76 (95% CI: 0.56, 1.03) respectively. Withdrawals due to GI AE (200/400mg) RR=0.92 (95% CI: 0.43, 1.97) and RR=0.52 (95% CI: 0.21, 1.29) respectively.</p>
<p>Searle 021 (73) DATA SUBMITTED COMMERCIAL IN CONFIDENCE</p>		
<p>Searle 042 (76) Celecoxib 2 x 100mg Diclofenac 2 x 50mg N= 687, 6 weeks, OA of hip or knee ACR functional capacity I-III Concomitant therapy >18 yoa</p>	<p>Patient and investigator global assessments Patient pain* OA severity Index Quality of Life (SF-36) GI and other adverse events</p>	<p>EFFICACY: both celecoxib and diclofenac produced significant improvements in primary OMs; diclofenac provided slightly greater efficacy, but difference based on Q-ratios was ≤12%.</p> <p>SAFETY: incidence of AEs lower for celecoxib, but significance of differences not reported. Total GI AE RR=0.64 (95% CI: 0.48, 0.86). Withdrawals due to GI AE RR=0.49 (95% CI: 0.21, 1.13).</p>
<p>Searle 054 (75) Geis 1999 (74) Celecoxib 2x50mg, 2x100mg or 2x200mg/day Naproxen 2x50mg/day N=843, 12 weeks, hip ACR functional class I-III >18 yoa</p>	<p>Patient and investigator global assessments Patient pain assessment* OA severity index WOMAC OA Index, APS pain score Quality of life (SF-36) Adverse events</p>	<p>EFFICACY: no SS differences between 100mg and 200mg bid celecoxib and naproxen; naproxen superior to 50mg in all OMs and some differences SS; no SS differences between 100mg and 200mg doses.</p> <p>SAFETY: no SS differences in AEs causing withdrawal; significance of differences in AEs not reported. Total GI AE (200/400mg) RR=0.81 (95% CI: 0.61, 1.07) and RR=0.84 (95% CI: 0.64, 1.11) respectively. Withdrawals due to GI AE (200/400mg) RR=0.41 (95% CI: 0.17,</p>

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
Study 118 (75) Celecoxib 2x100mg/day Diclofenac 3x50mg/day N=400, 6 weeks, knee ACR functional capacity I-III Concomitant therapy >18 yoa	Patient and investigator global assessments Patient assessments of pain* WOMAC OA index APS pain score OA severity index Adverse events	0.97) and RR=0.63 (95% CI: 0.30, 1.31) respectively. EFFICACY: no SS differences between celecoxib and diclofenac. SAFETY: diclofenac associated with more AEs, but statistical significance not reported. Total GI AE RR=0.71 (95% CI: 0.49, 1.05).

TABLE 23: CELECOXIB VS. PLACEBO FOR RHEUMATOID ARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Searle 012 (52) Simon 1998 (51) Celecoxib 2x40mg, 2x200mg or 2x400mg/day Placebo N=330, 4 weeks Steinbrocker functional capacity I-III CCX and DMARDs concomitant therapy permitted >18 yoa</p>	<p>Patient and investigator global assessments Patient pain assessment* ACR-20 responder index Joint swelling # joint tenderness/pain Duration morning stiffness Quality of life (SF-36) GI and other adverse events</p>	<p>EFFICACY: SS improvement in 200mg/400mg groups from placebo in patient global assessment ($p \leq 0.001$), # tender or painful joints ($p \leq 0.005$), and ACR criteria ($p \leq 0.025$); no SS differences between 40mg and placebo after week 1 in any OMs.</p> <p>SAFETY: incidence of AEs similar between groups, but significance of differences not reported. Total GI AE (400/800mg) RR=1.18 (95% CI: 0.62, 2.27) and RR=1.33 (95% CI: 0.71, 2.50) respectively.</p>
<p>Study 022 (57) Simon 1999 (54;55) Celecoxib 2x100mg, 2x200mg or 2x400mg/day Placebo N=923, 12 weeks ACR functional class I-III DMARDs and GCX permitted >18 yoa Paracetamol rescue</p>	<p>Patient and investigator global assessments (1-5) Patient pain* # painful/tender joints # swollen joints Duration morning stiffness ARC-20 responder index HAQ functional disability index Quality of life (SF-36) CRP Adverse events Incidence of ulcers and erosions by endoscopy</p>	<p>EFFICACY: SS improvement from baseline for all doses celecoxib cf placebo for all primary OMs, except for investigator global assessment at 100mg ($p < 0.05$); maximal effects by week 2 sustained through 12 weeks.</p> <p>SAFETY: incidence of endoscopically determined gastroduodenal ulcers not statistically different between groups ($p > 0.40$). Total GI AE (200/400/800mg) RR=1.41 (95% CI: 1.01, 1.97), RR=1.29 (95% CI: 0.91, 1.82) and RR=1.35 (95% CI: 0.96, 1.90) respectively. Withdrawals due to GI AE (200/400/800mg) RR=0.96 (95% CI: 0.20, 4.72), RR=2.29 (95% CI: 0.60, 8.76) and RR=2.13 (95% CI: 0.54, 8.41) respectively.</p>
<p>Searle 023 (53): DATA SUBMITTED COMMERCIAL IN CONFIDENCE</p>		

TABLE 24: CELECOXIB VS. NSAIDS FOR RHEUMATOID ARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Searle 022 (57) Simon 1999 (54) Celecoxib 2x100mg, 2x200mg or 2x400mg/day Naproxen 2 x 500mg/day N=917, 12 weeks ACR functional class I-III DMARDs and GCX permitted >18 yoa Paracetamol rescue</p>	<p>Patient and investigator global assessments (1-5) Patient pain* # painful/tender joints # swollen joints Duration morning stiffness ARC-20 responder index HAQ functional disability index Quality of life (SF-36) CRP Adverse events Incidence of ulcers and erosions by endoscopy</p>	<p>EFFICACY: no SS differences between celecoxib and naproxen, except greater efficacy of 200mg dose for patient and investigator global assessments (p<0.05).</p> <p>SAFETY: incidence of endoscopically determined gastroduodenal ulcers statistically greater for naproxen than celecoxib (p<0.001). Total GI AE (200/400/800mg) RR=0.90 (95% CI: 0.67, 1.19), RR=0.82 (95% CI: 0.61, 1.10) and RR=0.86 (95% CI: 0.64, 1.15) respectively. Withdrawals due to GI AE (200/400/800mg) RR=0.26 (95% CI: 0.07, 0.90), RR=0.61 (95% CI: 0.24, 1.54) and RR=0.57 (95% CI: 0.21, 1.50) respectively.</p>
<p>Searle 023 (53): DATA SUBMITTED COMMERCIAL IN CONFIDENCE</p>		
<p>Searle 041 Emery 1999 (58;59) Celecoxib 2 x 200mg/day Diclofenac 2 x 75mg/day SR N=655, 24 weeks ACR functional class I-III DMARDs/ CCX permitted (SS more patients receiving CCX on diclofenac than celecoxib) >18 yoa</p>	<p>Patient and investigator global assessments Pain score * # tender or painful joints # swollen joints Patient tenderness (0-3) Patient swelling (0-3) # patients responding to ACR-20 responder index HAQ functional disability score * Quality of life (SF-36) Duration morning stiffness Adverse events Incidence of ulcers and erosions by endoscopy</p>	<p>EFFICACY: no SS difference between groups in any OM, except celecoxib superior for #painful/tender joints at week 16.</p> <p>SAFETY: incidence of endoscopically determined gastroduodenal ulcers and withdrawal for GI-related adverse events statistically greater for diclofenac than celecoxib (p<0.001). Total GI AE RR=0.75 (95% CI: 0.62, 0.90). Withdrawals due to GI AE RR=0.36 (95% CI: 0.21, 0.60).</p>

TABLE 25: CELECOXIB VS. NSAIDS FOR RHEUMATOID AND OSTEOARTHRITIS

STUDY DETAILS	OUTCOME MEASURES	SUMMARY OF RESULTS
<p>Searle 062 (79) Burr 1999 (78) Celecoxib 2 x 200mg/day Naproxen 2 x 500mg/day N=537, 12 weeks, OA and RA ACR functional capacity I-III Concomitant therapy Paracetamol rescue >18 yoa</p>	<p>Patient and investigator global assessments Quality of life (SF-36) Adverse events Incidence of erosions and ulcers detected by endoscopy</p>	<p>EFFICACY: no SS differences in efficacy between groups.</p> <p>SAFETY: celecoxib associated with significantly lower incidence of gastroduodenal ulcers than naproxen ($p < 0.001$). Total GI AE RR=0.85 (95% CI: 0.68, 1.06). Withdrawals due to GI AE RR=0.68 (95% CI: 0.32, 1.44).</p>
<p>Searle 071 (80) : DATA SUBMITTED COMMERCIAL IN CONFIDENCE</p>		
<p>Searle 102 Silverstein, 2000 (77) Celecoxib 2x 400mg/day Diclofenac 2x75mg/day or Ibuprofen 3x800mg/day N=7968, 26-52 weeks, OA and RA >18 yoa 3 months disease duration Randomised 2:1:1 Aspirin up to 325mg/day permitted Concomitant DMARDS and GCX permitted</p>	<p>Patient and investigator global assessments Patient assessment of pain* HAQ functional disability index Quality of life (SF-36) Adverse events GI Adverse events Severity of dyspepsia Bleeding, perforation or obstruction Incidence of erosions and ulcers detected by endoscopy when presenting symptomatically</p>	<p>EFFICACY: not reported.</p> <p>SAFETY: significantly fewer GI adverse events for celecoxib group cf NSAID group ($p \leq 0.05$); celecoxib associated with significantly lower incidence of symptomatic ulcers and ulcer complications cf NSAIDs ($p = 0.02$). Withdrawals due to GI AE (vs diclofenac/ibuprofen) RR=0.70 (95% CI: 0.59, 0.82) and RR=0.90 (95% CI: 0.76, 1.07) respectively.</p>

3.5 SUMMARY OF ETODOLAC RESULTS

3.5.1 EFFICACY

3.5.1.1 *ETODOLAC versus PLACEBO*

- a. OA: Etodolac two four-week studies compare the efficacy of etodolac in OA, both showed etodolac to have superior efficacy although only included a total of 196 patients receiving placebo.
- b. RA: no evidence met inclusion criteria.

3.5.1.2 *ETODOLAC versus NSAID*

- a. OA: No differences between etodolac and any of the comparators examined except one study which included 270 patients that found etodolac to be superior to nabumetone in the treatment of OA of the knee as assessed by patients and investigators via global assessments ($p=0.009$) (15).
- b. RA: Of the three studies included that assessed the efficacy of etodolac in RA, the evidence suggests that etodolac is equivalent to aspirin and piroxicam over 1 year and 12 weeks respectively. However, there were problems with both trials as concomitant therapy including DMARDs and corticosteroids was permitted.

3.5.2 SAFETY

3.5.2.1 *ETODOLAC versus PLACEBO*

Evidence from only two studies including a total of 195 patients receiving etodolac at doses of either 600mg or 800mg per day and 196 receiving placebo. No differences were detected between the two comparators. Similar incidences of AEs overall in the over and under 65 age groups (see Table 11).

3.5.2.2 *ETODOLAC versus OTHER NSAIDS*

- a. Diclofenac: In both of the studies retrieved a trend was detected favouring etodolac, for total AEs and withdrawals due to AEs but it failed to reach significance (9;10). Neither study reported total GI events and the results from the GI withdrawals were conflicting, probably due to the small sample sizes of the two studies. Pooling data from the six and eight week results gives an overall risk ration of 0.89 (95% CI: 0.31,2.58) for GI withdrawals and 0.72 (95% CI :0.32, 1.61).
- b. Piroxicam: The four studies included provide conflicting results, with one study showing increased rates of AE withdrawals, Total AEs and GI withdrawals, although again the sample size was small(116 patients) (8). After twelve weeks total daily doses of 400mg and 600mg show a trend for superiority of etodolac for AE withdrawals and GI withdrawals although it does not reach significance. Pooled analysis of the two 600mg studies at 8 weeks also suggest superiority of etodolac with RR of 0.74 (95% CI: 0.41, 1.36) for GI withdrawals, 0.73 (95% CI: 0.50, 1.07) (12;14) for total GI AEs and 0.80 (95% CI: 0.49, 1.32) for AE withdrawals, but again this

difference is not significant except for total AEs RR 0.75 (95% CI: 0.56, 0.99) Figs 1.1, 1.2, 1.3, 1.4.

- c. Ibuprofen: Daily etodolac doses of 300mg and 1g produced a statistically significant lower rate of PUBs over 3 years in 1446 patients than ibuprofen affecting 2/620, 2/409 and 9/417 patients respectively RR= 0.23 (95% CI: 0.05, 1.04)(7).
- d. Other NSAIDs: Etodolac patients had fewer withdrawals due to AE than those treated with aspirin (RR=0.39 (95% CI: 0.27, 0.58) and experienced significantly less nausea, vomiting and abdominal pain ($p<0.05$). Trend for etodolac to be superior against nimesulide and tenoxicam for GI AEs (RR=0.81 (95% CI: 0.52, 1.27) and RR= 0.44((95% CI: 0.14, 1.37), although again not statistically significant, possibly due to the studies being underpowered.

3.5.3 OTHER EVIDENCE

3.5.3.1 There are several post marketing surveillance studies conducted in the UK, Italy, France and Switzerland to assess the efficacy and safety of etodolac. Despite inherent difficulties interpreting data in such studies, it may still give some valuable information about the effectiveness and the safety of the drugs in community settings.

Data from a total of 8,334 OA and RA patients who received oral doses of 200 and 600 mgs for periods ranging from 4 weeks to a year, have shown that the overall incidence of confirmed ulcers are low (83) (84), around 0.06 % (5 out of 8,334 people). In the long-term study conducted in the UK (1 year, n=543), this incidence rate was higher at 0.18%. In the French post marketing surveillance study (n=4,947) 1007 patients reported 1276 adverse events, of which almost half (50.5%) were considered unrelated to etodolac treatment. Adverse reactions led to discontinuation of therapy for 374 patients (7.6%). Only three patients (0.06%) had confirmed ulcers reported, but only two of those cases were considered treatment-related (85). Another large study (n=51,355) conducted in France has reported similar results; 9% of all patients withdrew from the study due to adverse events and the confirmed ulcer rate was 0.04% (22 cases) (85).

3.5.3.2 Schattenkirschner (84) reviewed safety data from 2,629 etodolac treated patients enrolled in 24 double-blind and open label RA and OA studies. Comparators in controlled studies included placebo, aspirin, sulindac, indomethacin, piroxicam, naproxen or ibuprofen. GI complaints were the most frequent amongst all new drug-related complaints; dyspepsia was reported in 13% of patients, abdominal pain 11%, nausea 8% and diarrhoea 6%. Overall, 171 patients (7%) withdrew prematurely because of GI complaints. 11 patients (0.3%) were diagnosed with GI ulcer or bleeding, all discontinued therapy. Adverse event profile (other than dyspepsia) was similar in patients over and under 65 years of age.

3.5.3.3 A clinical practice study involving 543 RA patients conducted in the UK found a similar frequency of adverse events as in clinical trials (86). In

the 162 patients (29.8%) who completed the trial, three serious drug-related adverse events were reported (two gastric ulcers and one thrombocytopenia), all recovered after appropriate treatment. There were no cases of GI haemorrhage. Additionally, there were no statistically significant differences in the rate of patient withdrawals from study by age or sex.

3.6 SUMMARY OF MELOXICAM RESULTS

In total, nine double-blind studies investigating the efficacy of meloxicam in OA have been included in this review. Only one included study compared meloxicam to placebo (26) and also included a diclofenac arm. Three studies compared meloxicam at licensed doses to piroxicam and five to modified release diclofenac. A total of 10,151 patients were randomised to meloxicam in the trials (154 3.75mg, 9,278 7.5mg and 719 15mg) plus 4,984 to diclofenac modified release and 153 diclofenac ordinary release, 4,612 to piroxicam, 157 to placebo. Six studies that examined meloxicam use in RA were located, none of which met the inclusion criteria for this review.

3.6.1 EFFICACY

3.6.1.1 *MELOXICAM versus PLACEBO*

Meloxicam at doses of 7.5mg and 15mg were shown to be superior to placebo over 12 weeks across all outcome measures. A dose response effect was observed on outcomes measured using the WOMAC scale (26).

3.6.1.2 *MELOXICAM versus NSAID*

The most robust evidence for meloxicam versus any other NSAID comes from a 4 week randomised controlled trial which included a total of 9323 patients randomised to either meloxicam 7.5mg or diclofenac 100mg SR per day (19). The results indicated that the two comparators had equal efficacy and although there was a trend in favour of diclofenac, it was small and the authors concluded it was unlikely to be clinically significant. Evidence from the SELECT study showed meloxicam 7.5mg to have equivalent efficacy to 20mg piroxicam over all outcomes (17).

3.6.2 SAFETY

3.6.2.1 *MELOXICAM versus PLACEBO*

Of the four safety outcomes evaluated, the only statistically significant difference between either meloxicam 7.5mg or 15mg and placebo was in the total AEs for the 15mg dose (RR= 1.21 (95% CI: 0.98, 1.49). The total withdrawals due to AE and due to GI AE both favoured placebo although did not reach significance for either dose (see Table 14). The point estimate for the total GI event rate, for both doses suggested equivalence, although the confidence interval included benefits for both comparators (Table 14).

3.6.2.2 *MELOXICAM versus OTHER NSAIDS*

Two studies were large randomised controlled trials that compared meloxicam to piroxicam (17) and diclofenac (19) which together included 17,979 patients and permitted tolerability analysis within clinically important high-risk subgroups. Meloxicam was associated with significantly fewer GI ADRs in women over the age of 65 against piroxicam (9% vs. 16% $p>0.001$) and diclofenac (12 vs. 20%), in patients receiving concomitant peptic ulcer prophylaxis (18 vs. 29%) and (21% v 28%), both $p<0.05$ and in patients on

cardiovascular medication 11 vs. 17% and 13 vs 20% , p<0.001. Patients with previous PUB had a lower incidence of GI ADRs 25% v 30% and 23% v 33%.

a. Diclofenac:

In 9323 patients randomised to either meloxicam 7.5mg or diclofenac 100mg SR per day(19), the meloxicam group reported fewer AEs [RR 0.86 (95% CI: 0.81, 0.92)], gastric AEs [RR 0.71 (95% CI: 0.64, 0.78)], withdrawals due to AEs RR 0.39 (95% CI: 0.59, 0.80) and withdrawals due to GI AEs RR 0.49 [(95% CI: 0.40, 0.60)] (all p<0.001). Of patients in the over 65 age group 13% of the meloxicam group experienced a GI AE compared to 19% in the diclofenac group [RR 0.68 (95% CI: 0.59, 0.79)]. The incidences in the under 65s were 12% and 16% respectively [RR 0.75 (95% CI: 0.66, 0.86)]. There were 5 PUBs in the meloxicam treatment arm and 7 in the diclofenac [RR 0.72 (95% CI: 0.23, 2.27)]. In addition 3 patients were hospitalised for a total of 5 days on meloxicam vs. 10 patients for 121 days diclofenac, which included 4 patients who spend a total of 31 days in intensive care. Four other studies also provide evidence to support the reduced incidence of GI events of meloxicam compared to diclofenac at licensed doses over at 4 (23), 6 (18), 12 (26) and 26 weeks (21) (Fig 2.1). Of the two studies that reported PUBs only one occurred in a patient receiving diclofenac (18) (Table 15).

b. Piroxicam:

The SELECT study found that 90% of patients randomised to meloxicam and 88% to piroxicam had good or satisfactory tolerance (51). The meloxicam group reported fewer AE [RR 0.80 (95% CI: 0.75, 0.87)], GI AE [RR 0.67 (95% CI: 0.60, 0.75)], (p<0.001), withdrawals due to GI AE [RR 0.72 (95% CI: 0.59, 0.88)] (p<0.01) and withdrawals due to AE [RR 0.85 (95% CI: 0.72, 0.99)] (17). Patients previously treated for peptic disease higher incidence of GI AEs, but lower in meloxicam group [RR 0.81 (95% CI: 0.60,1.10)]. PUBs 7 patients with meloxicam, 16 piroxicam [RR 0.44 (95% (95% CI: 0.18, 1.07)]. No difference in rate of serious AEs. Hospitalisations for GI AEs occurred in 6 meloxicam patients and 7 piroxicam for at total of 56 versus 121 days respectively. The evidence also suggests that meloxicam is superior to piroxicam after 26 weeks therapy for the total number of GI AEs reported RR=0.81 (95% CI: 0.60, 1.10) and withdrawals due to GI events RR= 0.61 (95% CI: 0.35, 1.06), although neither difference reaches significance.

3.6.3 OTHER EVIDENCE

3.6.3.1 An observational cohort study, was retrieved that compared patients receiving either meloxicam and or another NSAIDs. The two groups were of comparable age and sex and standard concomitant therapy was permissible (87). The evidence suggests that patients given meloxicam had higher baseline risks and tended to have worse disease

and tended to be non-responsive to prior NSAID therapy. There were greater statistically significant dropouts due to lack of efficacy but again may reflect resistance of patients subsequently receiving meloxicam to prior therapy. Overall there was a lower incidence of AE reporting, which must be considered with respect to the observational non-RCT nature of the study. Despite the preferential use of meloxicam in patients with a higher base-line risk, the RR of GI events in the two groups 0.56 (95% CI: 0.39, 0.82): $p=0.003$ (1.78 % vs. 3.16%) and PUB 0.30% compared to 0.00% $p=0.007$. Fewer meloxicam patients experienced dyspepsia, abdominal pain, gastritis or GI bleeding, although again the inherent limitations of the study design and grouping of other NSAIDs, with different baseline risks together must be considered. Logistic regression was used to adjust the RR for a GI AE by the influence of side-effects of previous NSAID therapy resulted in a risk estimate for the meloxicam group compared to the comparator NSAID of 0.49 (95% CI: 0.33, 0.74). There were no differences between the groups in terms of overall efficacy.

3.6.3.2 To evaluate whether patients who received meloxicam were at inherently greater baseline risk of GI events an evaluation using data from the General Practice Research Database (GPRD) was carried out (88). A random sample of 5000 patients receiving meloxicam was taken with 5000 age matched controls receiving ibuprofen, diclofenac, naproxen and 2500 receiving indomethacin. The results suggest that patients receiving meloxicam had a higher baseline risk than those receiving other NSAIDs. Baseline risk was defined as a history of diagnosis of dyspepsia, gastritis, duodenitis or peptic ulcer in pervious year and use of gastro-protective agents (antacids, H₂ blockers, proton-pump inhibitors), aspirin, other NSAIDs and oral corticosteroids either within the past six months or previously. Such patients were twice as likely to receive meloxicam (OR 1.9 to 2.4 and OR 2.2 to 2.8). The authors concluded that consequently patients receiving meloxicam would be expected to have higher rates of GI events than other commonly used NSAIDs based on baseline risk. This study associated the targeting of meloxicam to higher risk patients with claims of its lesser impact on GI tract offering theoretical safety advantages. This study emphasises that the underline baseline risk of populations being compared is important.

3.6.3.3 A second GPRD study compared 4359 patients receiving meloxicam with no previous NSAID in preceding year with a comparative sample of 10,000 patients receiving diclofenac, naproxen and piroxicam(89). For analysis of GI disease patients were excluded from the base population if they had been diagnosed with GI disorders prior to receipt of the first prescription for one of the study drugs. Four nested case-control studies were carried out with up to four controls (age, sex, practice, registration date and index date) identified for each case (2 for mild GI disease with exposure reduced to 30 days) who had been exposed within 90 days. No apparent differences although restricted by number of cases for serious GI disease. 11 cases of serious GI disease were reported yielding RR compared to diclofenac of 0 (CI uncalculable), 3.8 (95% CI: 0.3, 49.3) and 1.5 (95% CI: 0.2, 13.6) for meloxicam, naproxen

and piroxicam respectively). Similarly for mild GI disease the RR were 1.0 (95% CI: 0.5,1.7), 0.8 (95% CI: 0.6, 1.1) and 0.9 (95% CI: 0.7, 1.2).

3.6.3.4 A Prescription event monitoring study, in 19,087 patients receiving meloxicam between June and November 1997, identified 203 suspected ADRs to meloxicam were reported including 20 reports of GI haemorrhage, 7 melaena , 4 perforated duodenal ulcer and 5 uncomplicated peptic ulcer (90). Hypertension resulted in cessation of therapy in 6 patients and cardiac failure in 9 patients. Rates of GI upper haemorrhage 0.3 per 1000 months of exposure. Increased rates of dyspepsia, abdominal pain, peptic ulceration RR=4.0 (95% CI: 1.4, 13.2) were associated with prior upper GI disorder or who were prescribed concomitant gastro-protective agents.

3.6.3.5 One other meta-analysis was identified which included more studies as a result of the stricter restrictions on sample size, study duration and concomitant therapy used in this study (91). The additional studies included in Schoenfelds analysis that were excluded from this analysis included one which permitted concomitant intra-articular steroid injections (92), one which used suppositories (93) and two studies investigating efficacy of meloxicam in lumbago. Also included in the NICE analysis were three further studies (20;23;26). Meloxicam was shown to cause statistically fewer GI events than other NSAIDs in all analyses. Specifically GI AEs OR =0.64 (95% CI: 0.59,0.69), PUBs OR= 0.52 (95% CI: 0.28, 0.96), withdrawals due to GI events OR=0.59 (95% CI: 0.52, 0.67), and dyspepsia OR=0.73 (95% CI: 0.64, 0.84). The author however concluded that the inferences are limited by the method of detection used and the inherent limitations of meta-analysis.

3.6.3.6 Distel presented data from a systematic review of meloxicam data carried out by Boehringer Ingelheim in 1996 (94;95). It was however impossible to ascertain from either publication of this study, whether the data was obtained from studies already included in this systematic review as no references to included studies were given. The analysis included data from patients receiving IM, IV and rectal meloxicam in addition to oral from 34 Phase II/III studies and open-label, non-controlled phase I studies in healthy volunteers with various rheumatoid diseases and sciatica. The phase 3 trials included seven clinical trials in 1820 patients with OA and six studies in 1889 RA patients, most of which permitted concomitant corticosteroid therapy. The data from the RA and OA double-blind RCTs indicated that meloxicam had a reduced incidence of GI events, severe GI events, discontinuations due to GI events compared to piroxicam, diclofenac and naproxen $p < 0.05$. Diclofenac and naproxen also had a significantly increased incidence of upper GI adverse events, which included dyspepsia, eructation, nausea and vomiting. An interesting observation is that the incidence of upper GI events did not differ significantly between piroxicam and either 7.5mg or 15mg of meloxicam, which is at odds with other studies. Upper GI perforations occurred most frequently in patients treated with naproxen 750-1000mg (2.1%), followed by piroxicam 20mg (1.2%), diclofenac 100mg (0.6%), meloxicam 15mg

(0.2%) and meloxicam 7.5mg (0.1%), with the difference reaching significance in the cases of piroxicam and naproxen ($p < 0.05$). Higher incidence of PUBs in the elderly (>65 years) than in younger patients in all groups except meloxicam 7.5 mg, with diclofenac being better tolerated than piroxicam. The forest plots indicate that naproxen is the least tolerated with greatest total GI events over time, severe GI events over time.

3.6.3.7 Endoscopy studies: Two endoscopy studies in 44 (96) and 51 (97) healthy volunteers who received meloxicam 15mg/day versus piroxicam 20mg/day versus placebo and meloxicam 7.5mg/day versus 15mg/day versus piroxicam 20mg/day versus placebo. Both showed piroxicam to cause more gastric mucosal damage, which is consistent with epidemiological studies.

3.7 SUMMARY OF ROFECOXIB RESULTS

A total of 15 RCTs (8,740 patients) were located which investigated rofecoxib use in OA and a further 2 studies in RA (8,734) (27;28). The RA studies used a placebo control (28) and naproxen (27).

In the OA studies, the following comparators were used; placebo (2 studies), diclofenac (2), placebo plus NSAID (4 ibuprofen, 2 nabumetone, 1 naproxen/nabumetone), diclofenac/misoprostol (1) and celecoxib (3). Of these studies two evaluated safety only by endoscopic examination of patients (42) (43;44) and the results have therefore been considered separately. There have in addition been two pooled analyses published (98-100). All of the studies included in these analyses have been included in this updated systematic review.

Nine of the included RCTs have been published in full in peer-reviewed journals and seven as abstracts derived from conference proceedings. Further details from one unpublished study, previously published in abstract form, was provided by the manufacturer (35).

3.7.1 EFFICACY

3.7.1.1 *ROFECOXIB versus PLACEBO*

- a. OA: five studies were located which all found rofecoxib to be statistically significantly superior to placebo for all outcomes evaluated.
- b. RA: One dose ranging study which included a total of 658 patient was located (28) comparing rofecoxib 25 or 50 mg to placebo (28). All patients included were previously using NSAIDS in more than 25 out of the previous 30 days, and patients were also permitted to take second-line anti-rheumatic drugs and corticosteroids and methotrexate, although restricted to one third of patients entering the study. Analysis was stratified according to methotrexate use. Similar efficacy was found in methotrexate and non-methotrexate users. There was a similar incidence of ADRs in all groups except in the case of rash in 50mg group. Both the 25mg and 50mg produced statistically superior and clinically significant greater efficacy in the treatment of RA compared to placebo ($p=0.025$).

3.7.1.2 *ROFECOXIB versus NSAID*

- a. RA: The most robust evidence comes from a recent RCT which compared rofecoxib 50mg to naproxen 500mg bd in 8076 patients(27). The two interventions were shown to have equivalent efficacy in RA, although there is a trend favouring naproxen, which is not statistically significant.
- b. OA: One study showed a trend at one year suggesting superiority of diclofenac, which was statistically significant for two endpoints (patients assessment of response to therapy and physician's assessment of disease status (32). Evidence on the comparative efficacy in the over 80 age group over 6 weeks, 75% of whom had a history of cardiovascular disease indicates that the mean change in the patient assessment of disease status was smaller for nabumetone (-25.73 (12.5 mg rofecoxib) -25.01(25 mg rofecoxib) and -24.96 (1500mg

nabumetone) (48). Rofecoxib 25mg was also shown to be superior to ibuprofen for patient response to therapy and investigator global assessment of disease status ($p=0.05$) (33). Some evidence that has a faster onset of action and than nabumetone Geba (40), but equivalent to that of naproxen Laurenzi (45) but details only provided in abstract form.

3.7.2 SAFETY

There was very little information on either the total incidence of GI events or the withdrawals due to GI events in the included RCTs.

3.7.2.1 *ROFECOXIB versus PLACEBO [Fig 3.1a, 3.1b, 3.2]*

Only one study found any statistically significant difference in terms of total adverse event rates between rofecoxib 50mg and placebo after 24 weeks(42) $RR=0.73$ (95% CI: 0.63,0.85), which resulted in an overall pooled risk of 0.88 (95% CI: 0.88, 0.97) fixed effects when combined with the results of a second study(43). However, significant heterogeneity was detected between the studies and the pooled difference did not reach significance when random effects model was run [pooled $RR=0.89$ (95% CI: 0.61, 1.30)]. A more extensive meta-analysis of the total withdrawals due to AE events was possible (Fig 3.1c), which in all cases showed increased rate in the rofecoxib group, which reached significance only at the supra-therapeutic dose of 50mg over 24 weeks. Limited data on GI withdrawals or Total GI events was available from the individual studies and no pooled analysis was therefore possible. The results of the published meta- analysis are considered below.

3.7.2.2 *ROFECOXIB versus OTHER NSAIDS*

- a. Diclofenac: Rofecoxib had a superior withdrawal rate due to GI events compared to diclofenac, with the benefits being reduced at the 25mg dose (RR 12.5mg =0.47 (95% CI: 0.22, 1.02), 25mg=0.63 (95% CI: 0.31,1.26) (30). In terms of overall withdrawals, the pooled analysis after 1 year favoured rofecoxib, although this difference reduced at the 25mg dose when a random effects model was run as a result of significant heterogeneity being detected (Fig 3.3a, Fig 3.3b). Individual event rates were only reported for those occurring at a rate of 5% or more and the authors reported that the incidence was equivalent apart from the number of patients with abdominal pain, which was significantly greater in the diclofenac group ($p=0.01$). No difference was found in the total rate of AEs (32).
- b. Ibuprofen: The three studies that provided data suggested that rofecoxib had a similar rate of total AEs (33), with the pooled analysis of two studies (42;43)giving an overall RR of 1.02 (95% CI: 0.94,1.10) and 1.03 (95% CI: 0.96, 1.11). There were more withdrawals due to AEs in the ibuprofen group, which reached significance in the pooled analysis of 25mg at 24 weeks $RR=0.61$

(95% CI: 0.39, 0.97). The other pooled analyses results were 12.5mg 6 weeks RR =0.74 ((95% CI: 0.44, 1.27), 25mg 6 weeks RR= 0.80 (0.47, 1.36) and 50 mg 24 weeks RR= 0.94 (95% CI: 0.62, 1.42). The published pooled analysis indicated a superiority of rofecoxib in terms of discontinuations due to GI AE RR=0.73 (95% CI: 0.55, 0.97) (98) (101).

- c. Naproxen: The results of the large VIGOR (rofecoxib versus naproxen) study show a reduced risk with rofecoxib of confirmed upper GI event, complicated confirmed upper GI event, complicated upper GI bleeding and post duodenal bleeding (see Table 17) (27). The dose of rofecoxib used (50mg) is higher than that which is licensed for in OA patients. The benefits are reduced in patients with no previous glucocorticoid therapy at baseline RR 0.7 (95% CI: 0.4, 1.2), but not significant. Similarly the RR of clinical GI events in *H.pylori* negative and positive patients was significantly different (p=0.04, data not given). The RR of clinical GI events remained significantly lower in the sub-group of patients with very low risk (<65 yoa, *H.pylori* negative, no history of clinical GI event and not taking GCX at baseline) RR = 0.1 (95% CI: 0.02, 1.0). The authors concluded that 41 patients would have to be treated with rofecoxib in order to avert one clinical upper GI event. Other findings of interest were that the cardio-vascular death rate was 0.2% in both groups, with an incidence of myocardial infarction of 0.4% in the rofecoxib group compared to 0.1 % in the naproxen group (RR 0.2 (95% CI: 0.1, 0.7) with an excess in high risk patients in whom aspirin is indicated but not permitted to take due to trial protocol.
- d. Other NSAIDs: Although no details on efficacy provided, the study located concluded that rofecoxib and Arthrotec of similar efficacy, but in the rofecoxib group there were significantly fewer GI adverse events (28.9 vs. 48.5%, p<0.001) and significantly fewer patients with one or more episodes of diarrhoea (6.2 vs. 19.9%, p<0.001 (46). Rofecoxib had similar rates of total AEs and AE withdrawals compared to nabumetone (40;45), no data on total GI events were reported.

3.7.3 SUMMARY OF ROFECOXIB v CELECOXIB RESULTS

There are three head to head studies, involving a total of approximately 1,362 patients in existence none of which have been published and only very brief details were available. Geba et al compared the efficacy of rofecoxib (12.5 mg, 25 mg) celecoxib 200 mg and paracetamol 4000 mg/d in 379 OA patients(41). The main outcomes were; pain walking on flat surface (WOMAC Q1), pain at night (WOMAC Q3), pain at rest (WOMAC Q4), morning stiffness (WOMAC Q6) and patient global assessment of response to therapy. After 6 weeks of therapy, rofecoxib 25 mg qd was superior to paracetamol 4000 mg/d in almost all domains, where as it was superior to celecoxib 200 mg for night pain, pain at rest, percentage of patients with good or excellent response at week 4 and week

6, pain domain and stiffness domain. The incidences of GI events were not reported and no differences were found in the total event rates (Table 20).

There are two head-to head trials sponsored by Pharmacia, although the full reports are not yet available. In one RCT involving 182 OA patients compared the efficacy and safety of celecoxib with rofecoxib for 6 weeks. The results suggest that the efficacy in terms of measurement pain, stiffness and physical functioning of celecoxib was comparable with rofecoxib. The patients receiving 25mg rofecoxib experienced a greater incidence of GI events than those receiving celecoxib 200mg RR = 3.05 (95% CI: 1.39, 6.68), although the interpretation of these results needs to be considered with respect to the small sample size and different comparative doses. In the other trial 810 hypertensive OA patients over 65 years of age for 6 weeks: rofecoxib (25mg) associated with greater increases in oedema and systolic blood pressure compared to celecoxib (200mg) p<0.05.

3.7.4 SUMMARY OF OTHER EVIDENCE

3.7.4.1 Supplementary evidence comes from the pooled analysis of 8 phase 2b/3 studies of rofecoxib in patients with OA that have also been included in this review that has been recently published (98) [Table 26]. The results also include data from planned blinded extension studies, which have not been reported elsewhere. These results must therefore be considered within the context of the potential for bias that may have been introduced due to subjects stopping at the end of the stipulated trial period. This study found that rofecoxib had a reduced rate of withdrawals due to GI events than placebo RR 0.49 (95% 0.25, 0.98), with an increased rate due to withdrawals as a result of any AE RR=2.02 (95%:1.35, 3.02).

3.7.4.2 A second pooled analysis has investigated the overall incidence of thromboembolic cardiovascular events including events pertaining to cardiac (MI/angina), CNS (CVA, TIA) and peripheral (arterial embolism) systems (102). Data from 7535 patients was analysed which included 5,943 patients from 9 RCTs plus unpublished data from 1,592 patients with a mean treatment duration of 5.5 months. Similar rates of MI in all groups i.e. rofecoxib vs diclofenac, ibuprofen and nabumetone (NSAIDS that do not produce sustained maximal inhibition of platelet aggregation). Thrombotic events per 100 patients years were 2.9, 3.0 and 3.0 in the placebo, rofecoxib and NSAID treatment groups respectively. The incidence of cardiac, central nervous and peripheral system events were similar among the treatment groups and cardiovascular deaths per 100 patient years were 0.1 and 0.8 for rofecoxib and NSAIDS.

TABLE 26: RESULTS OF PUBLISHED POOLED ROFECOXIB ANALYSES (98) (101)

POOLED ANALYSIS	ROFECOXIB	NSAID	PLACEBO	TOTAL	RELATIVE RISK (95% CI)
# PATIENTS	3357	1564	514	5435	
DISCONTINUATION DUE TO ANY AE (%)	317 (9.4)	168(10.7)	24 (4.7)	509(9.4)	R v P: 2.02 (1.35, 3.02) R v NSAID:0.88 (0.74,1.05)
TOTAL PT YRS EXPOSURE	1428	615	112		
GI AE: discontinuation	118 (3.5)	75(4.8)	8(1.6)	201 (3.7)	R v P: 0.49 (0.25,0.98)
PUB	19	16	3	38	R v P: 0.97 (0.29, 3.27) R v NSAID:0.55 (0.28,1.07)
DISCONTINUATIONS (RATE / 100 PYR)					
GI AE					
6 months	10.42	15.84			0.68(0.5, 0.92)
12 months	8.2	12.03			0.70 (0.52,0.94)
DUE TO DYSPEPTIC AE					
6 months	5.41	8.85			0.64 (0.42,0.97)
12 months	4.20	6.34			0.69 (0.46,1.03)
DUE TO GI AE/ABDOMINAL PAIN					
6 months	11.93	18.4			0.67 (0.5,0.89)
12 months	9.32	13.98			0.69 (0.52,0.90)
DYSPEPTIC AE					
6 months	69.29	85.20			0.85 (0.74,0.97)
12 months	54.51	63.56			0.88 (0.78,1.01)
GI AE					
6 months	147.12	117.49			0.86 (0.78,0.95)
12 months	116.91	138.09			0.88 (0.80,0.97)
GI AE /ABDOMINAL PAIN					
6 months	154.61	190.87			0.85 (0.77,0.93)
12 months	122.50	148.44			0.86 (0.78,0.95)

6. 3.8 SUMMARY OF CELECOXIB RESULTS

Four studies of celecoxib in RA have been included in this review, of which one has not been published and the other three have six pertinent publications. One study included only a placebo control (51;52), two studies naproxen and placebo (53) (54;55;57) and one against diclofenac (58-60). Additionally, three further RCTs have evaluated patients with both RA and OA, the CLASS study against ibuprofen or diclofenac (77), one against naproxen or placebo, which has only been published in abstract form (78;79) and one unpublished study against diclofenac or placebo (80). This included a total of 10,346 patients receiving celecoxib, 1359 naproxen, 1994 placebo, 3252 diclofenac and 2331 ibuprofen. In addition, three pooled analyses have been published (82;103;104).

3.8.1 EFFICACY

3.8.1.1 *CELECOXIB versus PLACEBO*

Celecoxib was shown to be significantly superior to placebo in the treatment of both OA and RA

3.8.1.2 *CELECOXIB versus NSAID*

No clinically significant differences were found between the efficacy of celecoxib and any other NSAID in the treatment of either OA or RA.

3.8.2 SAFETY

3.8.2.1 *CELECOXIB versus PLACEBO [Figs 4.1, 4.2, 4.3 and 4.4]*

The pooled analyses presented in Appendix 3 indicate that at both four and six weeks, celecoxib at various doses shows no significant differences to the safety profile to placebo in terms of Total GI events. This difference reaches significance in favour of placebo for the 200mg, 400mg and 800mg doses at 12 weeks. The pooled RR for the difference are 1.22 (95% CI: 1.06,1.42), 1.25 (95% CI: 1.08, 1.44) and 1.35 (95% CI: 1.05, 1.74) respectively. No significant heterogeneity was detected between the studies. Celecoxib at doses of 200 mg and 400mg after 12 weeks of therapy was shown to have a significantly greater rate of GI withdrawals than placebo. Pooled RR= 1.67 (95% CI: 1.00, 2.79) and 1.71 (95% CI: 1.03, 2.85) respectively. No other significant differences were detected in the rate of GI withdrawals at other doses and timepoints. Overall rates of AEs and withdrawals due to AEs were significantly greater for celecoxib at 200 and 400mg doses after 12 weeks.

3.8.2.2 *CELECOXIB versus OTHER NSAIDS*

- a. Diclofenac: The studies indicate that celecoxib has a significantly superior GI safety profile to diclofenac (Fig 4.9). The pooled analysis for 200mg after six weeks gave as RR of total GI events of 0.67 (95% CI: 0.53, 0.84). Benefits in terms of total AEs and total withdrawals due to AEs were also significant(Fig 4.10 and 4.11). The CLASS study indicated that a supra-therapeutic dose of 800mg had significantly fewer GI events and withdrawals due to GI events

than diclofenac after 26 weeks RR=0.75 (95% CI: 0.62, 0.90) and 0.70 (95% CI: 0.59, 0.82) respectively.

- b. Ibuprofen: 400mg celecoxib produced significantly fewer total GI events and GI withdrawals than ibuprofen (RR=0.79 (95% CI: 0.65, 0.98) and RR=0.40 (95% CI: 0.20, 0.80)). A similar difference was detected for AE withdrawals and total AE events reported. The large CLASS study (7968 patients) indicated that celecoxib at a supra-therapeutic dose of 800mg had equivalent rates of AE withdrawals and GI withdrawals to ibuprofen RR =0.98 (95% CI: 0.87, 1.10) and RR =0.90 (95% CI: 0.76, 1.07) respectively.
- c. Naproxen: The pooled analysis indicates significantly fewer GI events, and GI withdrawals for celecoxib 200mg or 400mg at 12 weeks (Fig 4.5 and 4.7). No differences in the total AEs or withdrawals due to total AEs were detected (Fig 4.6, 4.8a and 4.8b).
- d. Combined diclofenac and ibuprofen: Data from the CLASS study for ibuprofen and diclofenac is combined. The annualised incidence of upper GI ulcer complications in celecoxib group was 0.76% (11 events/ 1441 patient years at risk) versus 1.45% (20/1384 patient-years) for patients taking either ibuprofen or diclofenac (p=0.09) (77). The relative risk was 0.53 (95% CI: 0.26, 1.11). For complications plus symptomatic ulcers the RR reduces to 0.59 (95% CI: 0.38, 0.94). However this included more than 20% of individuals taking low dose aspirin (\leq 325mg /day) in whom the annualised incidence of upper GI ulcer complications and combined symptomatic ulcers and ulcer complications was equivalent in the celecoxib and NSAID groups respective RR 0.95 (95% CI: 0.30, 2.98) and 0.77 (95% CI: 0.37, 1.60).

3.8.3 OTHER EVIDENCE

Bensen et al reported the data pooled from 5 RCTs, which have all been included in this analysis to assess the gastrointestinal tolerability of celecoxib compared with naproxen and placebo (103). A total of 5,615 OA and RA patients were enrolled in these studies for 12 weeks. The cumulative incidences of moderate to severe abdominal pain, dyspepsia, or nausea (composite endpoint) were: naproxen 500 mg (12.0%; 95% CI 9.9%-14.0%), celecoxib 50 mg bid (7.1%; 95% CI 5.0%-9.2%), celecoxib 100 mg bid (7.8%; 95% CI 6.0%-9.5%), celecoxib 200 mg bid (8.1%; 95% CI 6.4%-9.9%), celecoxib 400 mg bid (6.0%; 95% CI 3.6%-8.4%), and placebo (8.5%; 95% CI 6.5%-10.8%). After controlling for independent predictors of the composite endpoint, relative risks (RR) for the various treatments relative to naproxen 500 mg bid were: celecoxib 50 mg (RR 0.54; 95% CI 0.37-0.77; p < 0.001), celecoxib 100 mg (RR 0.60; 95% CI 0.45-0.80; p < 0.001), celecoxib 200 mg bid (RR 0.63; 95% CI 0.47-0.83; p = 0.001), celecoxib 400 mg bid (RR 0.56; 95% CI 0.35-0.89; p = 0.015), and placebo (RR 0.63; 95% CI 0.47-0.85; p = 0.002). The celecoxib group did not differ from placebo patients when reporting the composite endpoint, after controlling for independent predictors such as age, low dose aspirin use, history of GI ulcer or

NSAID intolerance, sex, VAS pain and ethnicity. The authors concluded that the upper GI tolerability of celecoxib is superior to naproxen.

In another recent review, Goldstein et al has reported on 14 RCTs and one open-label trial involving over 11,000 patients (104). Again all of the studies have been included in this review. The comparator arms included placebo, naproxen, ibuprofen and diclofenac. The principal outcome measure was UGI ulcer complications defined as bleeding, perforation, or gastric outlet obstruction. In the RCTs, UGI ulcer complications occurred in no placebo patients (0 of 1,864 patients), in 2 of 6,376 celecoxib patients (0.03%), and in 9 of 2,768 patients receiving an NSAID (0.33%), corresponding to annual incidences of 0.20% for celecoxib ($p > 0.05$ vs. placebo) and 1.68% for NSAIDs ($p = 0.002$ vs. celecoxib and placebo). The incidence of ulcer complications was 0.17% (9/5155) in the long-term open-label trial (annualised incidence: 0.18%). The authors concluded that the incidence of UGI ulcer complications associated with celecoxib was statistically significantly lower than with conventional NSAIDs (ibuprofen, naproxen or diclofenac), but similar to that in patients in placebo group.

4. ESTIMATE OF BUDGETARY IMPACT

The cost impact analysis presented in the original report assumes that 1,575,000–2,250,000 arthritis patients would be treated with Cox II selective inhibitors⁵⁰. However, as stated in the original document, this may be an overestimate for the following reasons:

- 1) Not all OA and RA patients are candidates for Cox II inhibitors as some patients may be offered other treatments prior to Cox II inhibitors. Therefore, the stated figures refer to the “ceiling” expenditure and may not be fully realised.
- 2) The current expenditure figures are based on the average cost of NSAID. However, because some of the Cox II selective drugs have already established markets, the baseline expenditure may be slightly higher than the analysis suggests. This may again mean that the cost forecast has been overestimated.
- 3) The relative reduction across different risk groups was assumed to be constant due to a lack of appropriate data. Therefore, the cost estimates for high-risk groups (reported in Table 4.17) may also be overestimates.

The original report calculated the iatrogenic cost factor for meloxicam to be 2.45 using the data from the 6-month model submitted by the manufacturer. This figure was discounted to “2” in line with other NSAIDs based on the assumption that meloxicam has a better GI safety profile compared with standard NSAIDs and therefore should not cause more expenditure than standard NSAIDs. However, the manufacturer claims that the 6-month model (meloxicam vs rofecoxib) was deliberately loaded against meloxicam to prove cost-effectiveness, and this may indeed explain the high cost factor for meloxicam.

The iatrogenic cost factor (including all side effects) for meloxicam using the 4-week model was calculated to be 3.24. However, this reduced to 1.9 when only GI adverse effects were taken into consideration⁵¹. If was then assumed this value to be the iatrogenic cost factor for meloxicam (instead of 2.45 derived from the 6-month model), the total daily cost for meloxicam reduced to £0.63 instead of £0.81 and switching all NSAID prescriptions for OA treatment to meloxicam would cost the NHS approximately £7,155,000 -£9,450,000 (in contrast to the figures reported in Table 4.13).

⁵⁰ In page 79, para 2 of the original report, the prevalence estimate of 1,350,000 should be 1,325,000, which is the value used in the calculations and the rest of this text. Therefore this does not alter the calculations, and hence the conclusions.

⁵¹ $(£149 * 0.118) / (£0.33 * 28) = 1.9$

5. ISSUES FOR CONSIDERATION

In this report the data for different doses of drugs and for different types of NSAID in the comparator arm have been separated, as there is evidence to suggest that individual NSAIDs have different toxicity profiles. Meta-analyses of NSAID associated toxicity have demonstrated that low dose ibuprofen carries the lowest risk of GI complications with comparative relative risks of 2 for fenoprofen, aspirin and diclofenac and 2-3 for sulindac, diflusal, naproxen, indomethacin and tolmetin and above 3 by piroxicam, ketoprofen and azopropazone (105). Another study conducted using the GPRD database found that ibuprofen again was associated with the lowest RR of UGIB 2.9 (95% CI: 1.7, 5.0), naproxen 3.1 (95% CI: 1.7, 5.9) and diclofenac 3.9 (95% CI: 2.3, 6.5) and azopropazone and piroxicam having a RR of 18 and 23.4 respectively (88).

The use of different doses may similarly affect the outcomes of comparisons and they have therefore been considered separately. Epidemiological studies have shown that GI toxicity varies by a factor of 3 to 10 over the ranges of recommended doses, depending on the NSAID under investigation (88;106). High doses are more toxic than lower doses with the OR for NSAID associated ulcer complications ranging from 2.5 on low to 8.5 on high (106) ibuprofen and indomethacin, independent of duration of exposure(88).

The likelihood of detecting an adverse drug reaction (ADR) is dependent on its severity, frequency and occurrence relative to exposure. A number of sources are used to collate information on ADRs which include pre-marketing clinical trials, case reports, spontaneous reporting systems, computerised patient databases (e.g. GPRD) and post-marketing studies. Although the RCT is the gold-standard of clinical trial designs, the numbers of patients used and the short duration mean that they will only identify the most common and acutely occurring ADRS within the specified subgroup of included patients. Moreover, trial protocols exclude patients from 'at risk' groups which are not generalisable to the population who will inevitably be exposed to the drug (i.e. people with co-morbidity). As many RCTs are not powered sufficiently to detect differences in rare events such as PUBs and the definition of PUB (perforations, ulcers and bleedings) varied across the included studies, this review has not pooled rates of PUBs from individual clinical trials but has presented the results separately. The data from endoscoped studies have also been abstracted but consideration must be given to the fact that the link between endoscopically detected ulcers and clinical symptoms has not been fully described and gastrointestinal symptoms are often poorly correlated with endoscopic findings (107) (108).

Spontaneous reporting systems such as the Yellow Card system and the MedWatch system in the United States are modern extensions of the system of case. Both suffer from similar disadvantages in that the number of adverse events that are recorded are a function of the length of time that a drug has been on the market, the amount it is prescribed, the seriousness of the event and the attending publicity. Neither method can be used to calculate incidences or relative safety, as the size of exposed population is generally not known and must be estimated from prescription data. In the majority of instances, neither system is able to conclusively prove causality. Due to these disadvantages both

methods are more useful for providing information on unusual or rare events, occurring during the initial or long-term use of a drug, than detecting increases in common events or events that occur remotely in time from the medication use (109).

In this review we have also mentioned several post-marketing studies, especially for meloxicam and etodolac. Post-marketing pharmacoepidemiologic studies, using cohorts and information obtained from computerised databases, are increasingly used to evaluate drug safety as they permit the assessment of risk factors and the control of potential confounders to a greater extent than spontaneous reports(109). Such studies are therefore able to elucidate adverse events that may be relatively common in both exposed and unexposed populations but occur with increased frequency after drug exposure. Although post-marketing studies have many advantages over other methods of ADR evaluation, there are inherent problems in the analysis and interpretation of the results, as drug exposure and confounding factors will vary over the length of long-term observational study. The usefulness of the information derived from computerised database is also highly dependent on the accuracy and completeness of data collection and entry, which needs to be rigorously controlled and monitored.

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APPENDIX I: SEARCH STRATEGIES

Medline 1966 – December week 4 2000 (via OVID, Biomed)

- #1 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenasell).ti, ab
- #2 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenasell).ti, ab
- #3 (cox-2 or cox2 or cox-II or coxII).ti, ab
- #4 (rofecoxib or vioxx or MK-0966).mp
- #5 (celecoxib or celebrex or SC-58635).mp
- #6 (meloxicam or mobic).mp
- #7 (etodolac or lodine or ultradol).mp
- #8 *Cyclooxygenase inhibitors/
- #9 *Etodolac/
- #10 or/1-9
- #11 arthrit\$ or osteoarthritis\$
- #12 exp *Arthritis/
- #13 11 or 12
- #14 10 and 13

combined with Cochrane rct filter and NHS CRD economic evaluation filter.

Cochrane Controlled Trials Register (CCTR) (Issue 4: 2000)

- #1 cyclooxygenase*
- #2 "cyclo oxygenase*"
- #3 cox*
- #4 rofecoxib or vioxx
- #5 celecoxib or celebrex
- #6 meloxicam or mobic
- #7 etodolac or lodine or ultradol
- #8 cyclooxygenase-inhibitors:ME
- #9 etodolac:ME
- #10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
- #11 arthrit* or osteoarthritis*
- #12 arthritis*:ME
- #13 #11 or #12
- #14 #10 and #13

Embase (1980 – December 2000, via Silverplatter)

- 1 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenasell) in ti, ab
- 2 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenasell) in ti, ab
- 3 (cox-2 or cox2 or cox-II or coxII) in ti, ab
- 4 (rofecoxib or vioxx or MK-0966) in ti, ab, mn, tn
- 5 (celecoxib or celebrex or SC-58635) in ti, ab, mn, tn
- 6 (meloxicam or mobic) in ti, ab, mn, tn
- 7 (etodolac or lodine or ultradol) in ti, ab, mn, tn
- 8 "cyclooxygenase-2-inhibitor"/ all subheadings
- 9 "cyclooxygenase-2"/ all subheadings
- 10 "celecoxib"/ all subheadings
- 11 "meloxicam"/ all subheadings
- 12 "etodolac"/ all subheadings
- 13 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
- 14 arthrit*
- 15 osteoarthritis*
- 16 (arthrit* or osteoarthritis*) in ti, ab
- 17 explode "arthrits"/ all subheadings
- 18 #16 or #17
- 19 #13 and #18

Appendix II: EXCLUDED STUDIES

ETODOLAC

STUDY	8. REASON FOR EXCLUSION
Andelman, 1983(110)	Unlicensed subtherapeutic dose
Bacon, 1990(111)	Review
Bacon, 1994(112)	Review
Bianchi Porro, 1991(113)	Unlicensed subtherapeutic dose
Brasseur, 1991 (114)	Inadequate sample size
Briancon, 1991(115)	Unlicensed subtherapeutic dose
Burssens, 1993(116)	Inadequate sample size
Chikanza, 1997(117)	Inadequate sample size
Ciampi, 1989(118)	Inadequate sample size
Delcambre, 1990 (119)	Review
De Querois, 1991(120)	Unlicensed subtherapeutic dose
Del Toro, 1983(121)	Unlicensed subtherapeutic dose
Dick, 1993(122)	Unlicensed subtherapeutic dose
Dore, 1995(123)	Unlicensed subtherapeutic dose
Edwards, 1983(124)	Unlicensed subtherapeutic dose
Fioravanti, 1989(125)	Unlicensed subtherapeutic dose, inadequate sample size, inadequate duration
Freitas, 1990(126)	Inadequate sample size
Gordon, 1983 (127)	Unlicensed subtherapeutic dose
Jacob, 1983(128)	Unlicensed subtherapeutic dose
Jacob, 1985b(129)	Unlicensed subtherapeutic dose
Jacob, 1986(130)	Unlicensed subtherapeutic dose
Jennings, 1997(131)	Inadequate sample size
Jubb, 1992(132)	Inadequate sample size
Karaoglan, 1995(133)	Inadequate sample size
Karbowski, 1991(134)	Inadequate sample size
Khan, 1992(135)	Inadequate sample size
Lonauer, 1993(136)	Unlicensed subtherapeutic dose
Mejjad, 2000(137)	Unlicensed subtherapeutic dose, Inadequate sample size
Palferman, 1991(138)	Inadequate sample size
Pena, 1991(139)	Inadequate sample size
Perpignano, 1991 (140)	Inadequate sample size
Platt, 1989(141)	Interim analysis
Porzio, 1993(142)	Inadequate sample size
Russell, 1990(143)	Inadequate sample size
Sanda, 1983(144)	Inadequate sample size
Schattenkirchner, 1991(145)	Unlicensed subtherapeutic dose
Taha, 1990(146)	Inadequate sample size
Taha, 1989(147)	Inadequate sample size
Vetter, 1982(148)	Inadequate sample size
Waltham-Weeks, 1987(149)	Unlicensed subtherapeutic dose
Waterworth, 1992(150)	Inadequate sample size

CELECOXIB

STUDY	REASON FOR EXCLUSION
Lanza, 1997(151)	healthy participants
Leese, 2000(152)	healthy participants
Lipsky, 1997(153)	Reporting results from Simon, 1998 (51)
Malmstrom, 1999(154)	dental pain
Mengle-Law, 1997(155)	healthy participants
Searle 013(156)	inadequate duration
Singh, 1999(157)	non-randomised uncontrolled study

9.

10. ROFECOXIB

STUDY	REASON FOR EXCLUSION
Bjarnason(158)	Healthy volunteers
Lanza, (159)	healthy volunteers with endpoints of impact on mucosal endpoints
Malmstrom, 1999(154)	dental pain

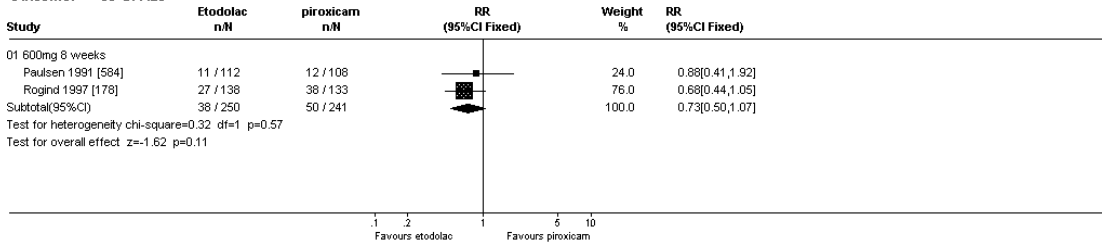
11. MELOXICAM

STUDY	REASON FOR EXCLUSION
Bevis, 1996(58)	uncontrolled, inadequate sample size
Carrabba, 1995 (93)	rectal administration & inadequate duration: 3 weeks
Degner, 2000(87)	observational uncontrolled phase4
Distel, 1996(94;95)	systematic review
Ghozlan, 1996(160)	Intramuscular administration
Hosie, 1998(161)	uncontrolled observational study
Huskisson, 1994(162)	Inadequate duration: 3 weeks
Lemmel, 1997 (163-165)	Inadequate duration: 3 weeks
Lipscomb (97)	Endoscopy healthy volunteers
Lund, 1998(164)	Inadequate duration: 3 weeks
Mazor, 1998(166)	Inadequate duration: 3 weeks
Patoia, 1996(96)	Endoscopy healthy volunteers
Prouse, 1996(167)	uncontrolled
Reginster, 1996(168)	Inadequate duration: 3 weeks
Tsubouchi, 2000(169)	In-vivo study
Valat, 1998(163)	Inadequate duration: 2 weeks
Wojtulewski, 1996(92)	concomitant therapy

APPENDIX III

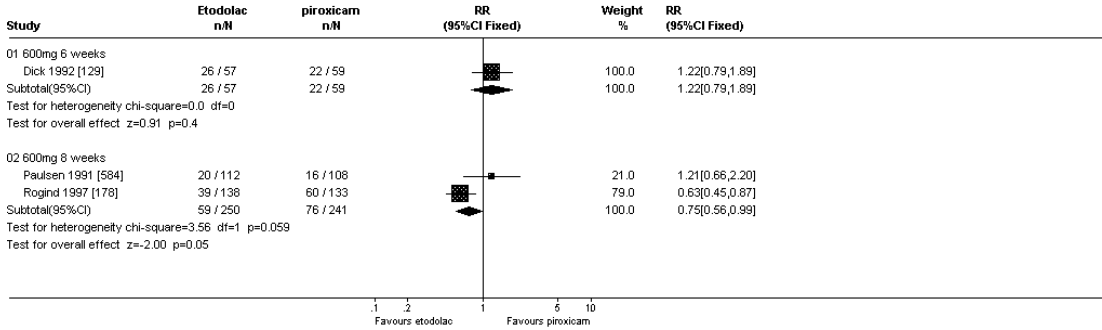
FIG 1.1

Comparison: 02 Etodolac versus piroxicam
Outcome: 03 GI AEs



12. FIG 1.2

Comparison: 02 etodolac versus piroxicam
Outcome: 02 TOTAL AEs



13. FIG 1.3

Comparison: 02 Etodolac versus piroxicam
Outcome: 04 GI withdrawals

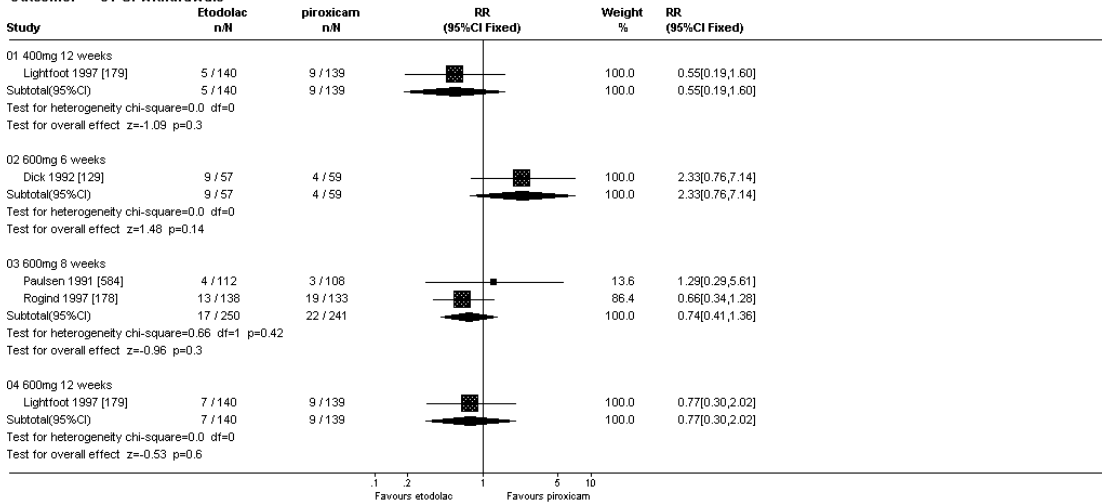
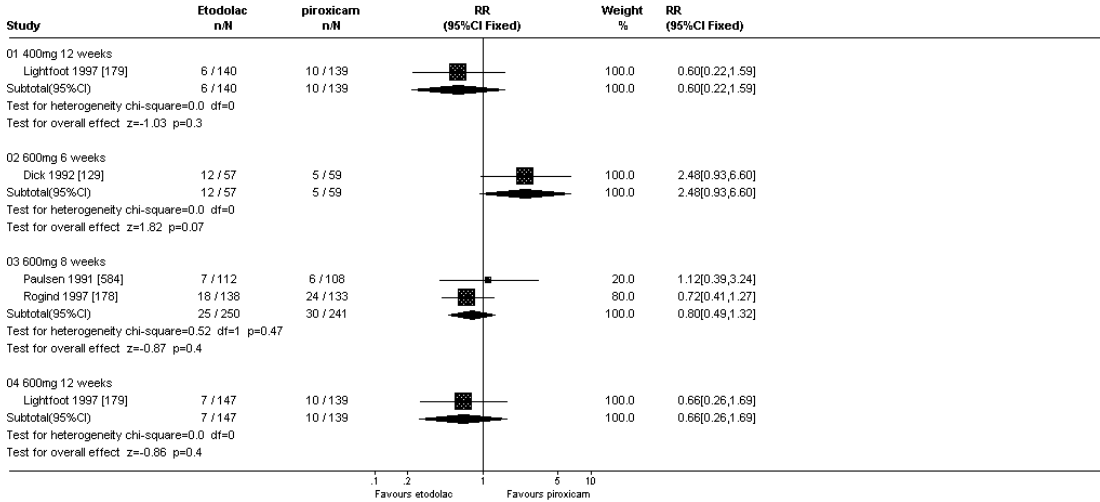


FIG 1.4

Comparison: 02 etodolac versus piroxicam
Outcome: 01 AE withdrawals



13.1. FIG 2.1

Comparison: 07 meloxicam versus diclofenac
Outcome: 03 GI AEs

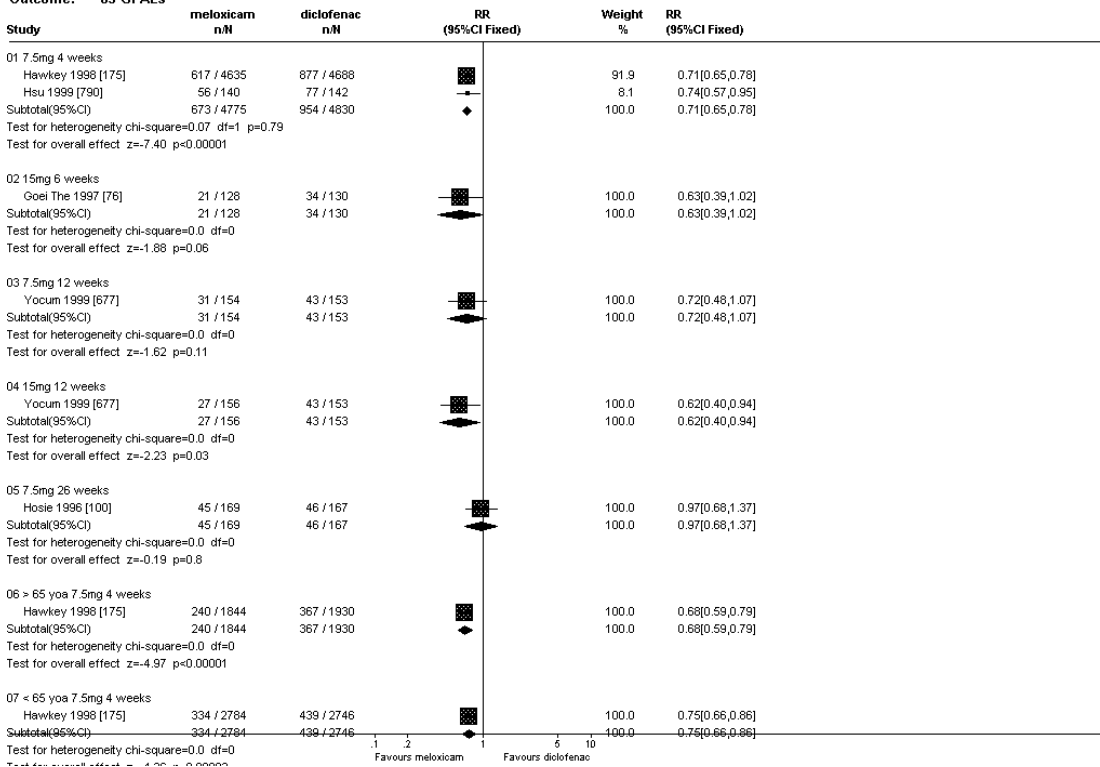
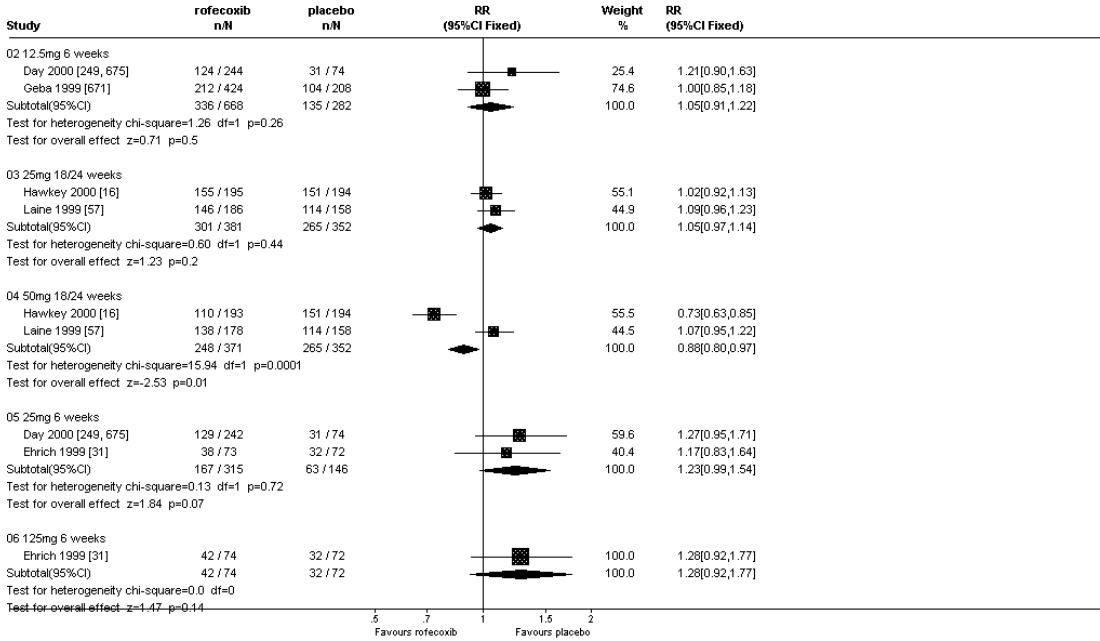


FIG 3.1a

Comparison: 17 rofecoxib versus placebo
Outcome: 01 TOTAL AES



13.2. FIG 3.1b

Comparison: 17 rofecoxib versus placebo
Outcome: 01 TOTAL AES

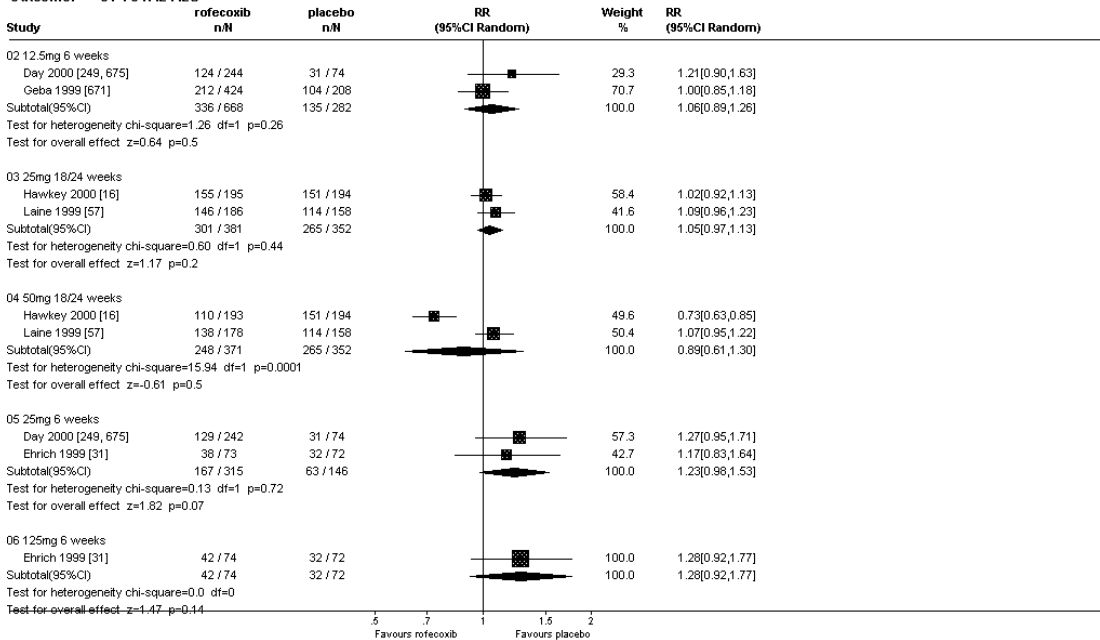


FIG 3.2

Comparison: 17 rofecoxib versus placebo
Outcome: 02 AE withdrawals

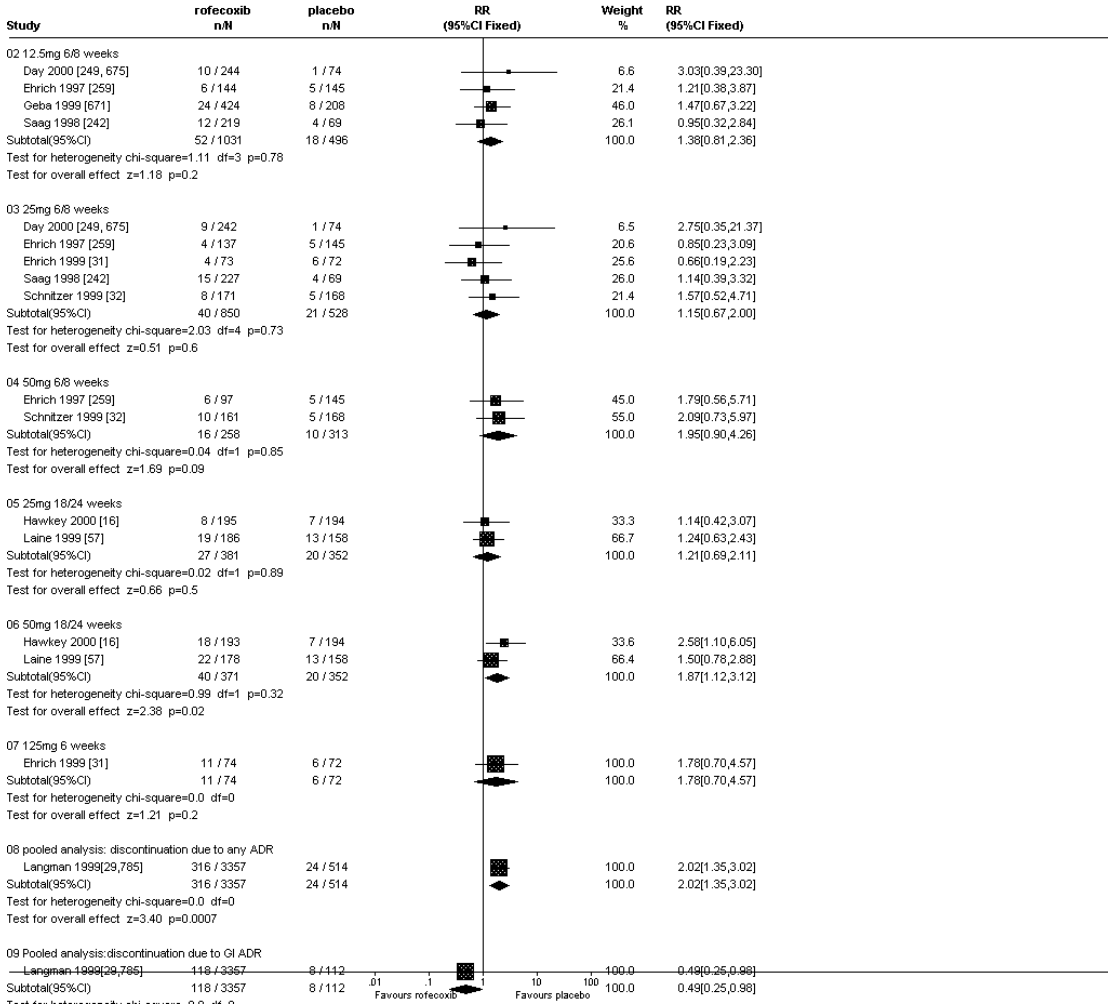


FIG 3.3a

Comparison: 20 rofecoxib versus diclofenac
Outcome: 02 AE withdrawals

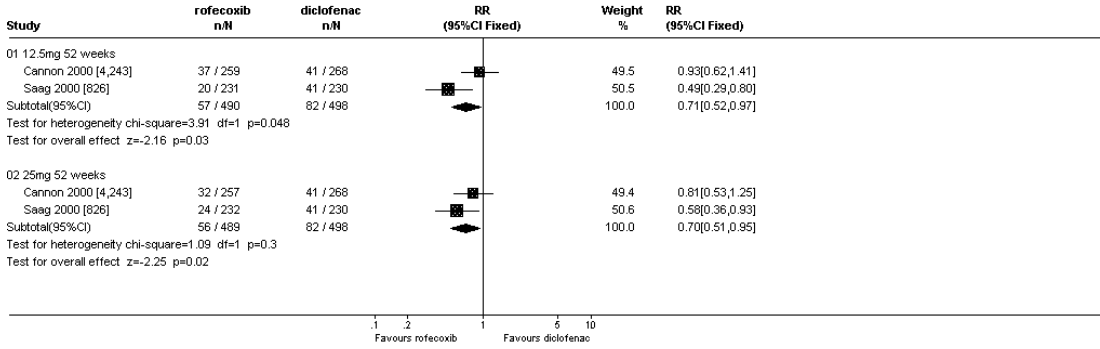


FIG 3.3b

Comparison: 20 rofecoxib versus diclofenac
Outcome: 02 AE withdrawals

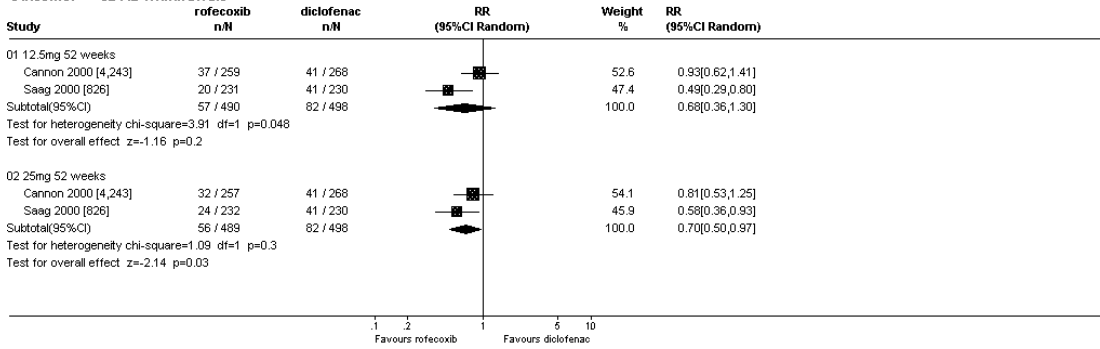


FIG 4.1

CELECOXIB VERSUS PLACEBO: TOTAL GASTRO-INTESTINAL ADVERSE EVENTS
REMOVED: DATA SUBMITTED COMMERCIAL IN CONFIDENCE

FIG 4.2

CELECOXIB VERSUS PLACEBO: TOTAL ADVERSE EVENTS
REMOVED: DATA SUBMITTED COMMERCIAL IN CONFIDENCE

FIG 4.3

CELECOXIB VERSUS PLACEBO: WITHDRAWALS DUE TO GASTRO-INTESTINAL
ADVERSE EVENTS
REMOVED: DATA SUBMITTED COMMERCIAL IN CONFIDENCE

FIG 4.4

CELECOXIB VERSUS PLACEBO: WITHDRAWALS DUE TO ADVERSE EVENTS
REMOVED: DATA SUBMITTED COMMERCIAL IN CONFIDENCE

FIG 4.5

CELECOXIB VERSUS NAPROXEN: TOTAL GASTRO-INTESTINAL ADVERSE EVENTS
REMOVED: DATA SUBMITTED COMMERCIAL IN CONFIDENCE

FIG 4.6

CELECOXIB VERSUS NAPROXEN: TOTAL ADVERSE EVENTS
REMOVED: DATA SUBMITTED COMMERCIAL IN CONFIDENCE

FIG 4.7

CELECOXIB VERSUS NAPROXEN: WITHDRAWALS DUE TO GASTRO-INTESTINAL
ADVERSE EVENTS
REMOVED: DATA SUBMITTED COMMERCIAL IN CONFIDENCE

FIG 4.8a

CELECOXIB VERSUS NAPROXEN: WITHDRAWALS DUE TO ADVERSE EVENTS
(FIXED EFFECT)
REMOVED: DATA SUBMITTED COMMERCIAL IN CONFIDENCE

FIG 4.8b

CELECOXIB VERSUS NAPROXEN: WITHDRAWALS DUE TO ADVERSE EVENTS
(RANDOM EFFECT)
REMOVED: DATA SUBMITTED COMMERCIAL IN CONFIDENCE

FIG 4.9

CELECOXIB VERSUS DICLOFENAC: TOTAL GASTRO-INTESTINAL ADVERSE
EVENTS
REMOVED: DATA SUBMITTED COMMERCIAL IN CONFIDENCE

FIG 4.10

CELECOXIB VERSUS DICLOFENAC: TOTAL ADVERSE EVENTS
REMOVED: DATA SUBMITTED COMMERCIAL IN CONFIDENCE

FIG 4.11

CELECOXIB VERSUS DICLOFENAC: WITHDRAWALS DUE TO ADVERSE EVENTS
REMOVED: DATA SUBMITTED COMMERCIAL IN CONFIDENCE