

Appendices

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

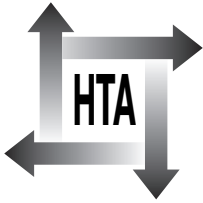
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Appendix I

Review of existing systematic reviews

Characteristics of the included reviews

The characteristics of included systematic reviews are summarised in *Table 103*. Of the completed reviews, 13 evaluated celecoxib, five etodolac, seven meloxicam, 11 rofecoxib and one valdecoxib. No systematic reviews for lumiracoxib or etoricoxib were found. All reviews evaluated use in patients with RA or OA. Some reviews also included other pain-related conditions such as dental pain and primary dysmenorrhoea. Four reviews evaluated use in patients with RA only and four in patients with OA only. Thirteen reviews evaluated both efficacy and safety outcomes, five focused on tolerability and safety (GI safety in all cases but one) and two on efficacy.

Twelve reviews were narrative reports: providing a qualitative synthesis of included studies. Only six undertook a meta-analysis.^{53,120,121,124,125,130} The remaining two planned a meta-analysis but did not do so because of insufficient data.^{112,118}

Quality of reviews

The quality of reviews was assessed according to Oxman and Guyatt's criteria.³²⁸ These criteria assess the adherence of a review to scientific principles known to reduce bias. An overall score is assigned out of 7, where 1 represents 'extensive flaws in the scientific quality of the overview', 3 'major flaws', 5 'minor flaws' and 7 'minimal flaws'.

The quality of included reviews is summarised in *Table 103*. Most included reviews scored 3 (four reviews) or 4 (six reviews) – indicating major or moderate flaws. These were related to potential bias in the selection of studies,^{119,122} publication,^{120,128} language,^{113,116,120,123,124,126,128} geographical bias,¹¹³ lack of evaluation and analysis of the quality of included studies^{113,116,120,121} and lack, or only partial reporting, of methods for combining data from studies.^{113,119,122–124,126,128} For example, the review by Deeks and colleagues of celecoxib⁵³ was methodologically of very high quality but failed to identify different publications as originating from

the same study population and might have pooled duplicate data from these same studies, leading to bias.

A further five reviews^{114,115,117,127,129} scored 2 on quality assessment, indicating major flaws. These poor-quality reviews did not show clearly a comprehensive search strategy or that precise inclusion criteria had been applied.

Overall, only four of the included reviews were considered to be of the highest quality (i.e. quality score of 7).^{112,118,125,130}

Results

Efficacy

All reviews gave a narrative of efficacy data: Deeks and colleagues⁵³ did a meta-analysis – the pooled summary estimates from this study might be prone to bias as discussed above. Nevertheless this review, like others, concluded that the efficacy of celecoxib was similar to non-selective NSAIDs. Most reviews, except that by Emery and colleagues,¹²³ separated OA and RA patients and since outcome measures and patient characteristics may differ, substantial pooling may not be appropriate.

Eleven reviews^{53,112,113,115,117–119,123,129,130,329} evaluated the efficacy of COX-2 selective NSAIDs for RA, seven celecoxib,^{53,112,113,115,126,129,130} two etodolac,^{123,130} four meloxicam,^{113,115,123,130} six rofecoxib,^{113,115,117,118,129,130} and one valdecoxib.¹¹⁹

Eleven reviews^{53,113–115,117,119,123,124,127,128,130} evaluated the efficacy of COX-2 selective NSAIDs for OA; six celecoxib,^{53,113–115,127,130} four etodolac,^{123,124,128,130} four meloxicam,^{113,115,123,130} six rofecoxib^{113–115,117,127,130} and one valdecoxib.¹¹⁹

Emery and colleagues¹²³ evaluated the relationship between NSAID dose, for etodolac, meloxicam and non-selective NSAIDs, and efficacy in patients with RA or OA. Overall meloxicam 7.5 and 15 mg were considered more effective than placebo with the 15-mg dose superior to the 7.5-mg dose for efficacy. Results for etodolac were less clear. One trial suggested improved efficacy

TABLE 103 Characteristics of included systematic reviews

Review	COX-2 evaluated	Disease population	Outcome domains	Number of trials included (n = patients) ^a	Meta-analysis	Quality score ^b	Comments
Ashcroft, 2001 ²¹	Celecoxib	RA and OA	Safety – GI	5 (n = 4632)	Yes	4	Included RCTs with scheduled endoscopies to evaluate the incidence of endoscopic gastroduodenal ulcers. Pooled estimates as RRs. If χ^2 test for heterogeneity < 0.5 random effects used. Some of the analyses represent the results of single trials. Sensitivity analysis undertaken
Chavez, 2003 ¹¹⁹	Valdecoxib	Any	Efficacy Safety Pharmacology Kinetics	RA and OA 7 (n = 6385) + 2 Syst Rev	No	3	Narrative review. Types of studies included not specified (majority were abstracts). Table of incidence of AEs across studies is presented but only selective studies are included
de Vries, 2002 ¹²²	Celecoxib Rofecoxib Meloxicam Etodolac	RA and OA	Safety – GI	2 celecoxib (n = 1137) 1 rofecoxib (n = 483) 3 meloxicam (n = 1075) + 1 Syst Rev (NICE)	No	4	Included RCTs and systematic reviews. Results of NICE review summarised plus results of six subsequently published RCTs (1 was a second report of a trial included in the NICE review)
Deeks, 2002 ⁵³	Celecoxib	RA and OA	Efficacy Safety Tolerability	9 (n = 15,187)	Yes	4	Systematic review of RCTs (published and unpublished). Data included from manufacturers' reports of industry-sponsored trials Separate meta-analyses undertaken for each comparison and outcome. Duplicate data from separate publications might have been combined inappropriately
El Desoky, 2001 ¹²⁹	Celecoxib Rofecoxib	RA	Efficacy Safety Kinetics Interactions	3 celecoxib (n > 8700) + 2 Syst Rev + manu info 0 rofecoxib + manu info	No	2	Narrative review of English language publications. Types of studies not specified. Considered many other treatment options
Emery, 2002 ¹²³	Meloxicam Etodolac	RA and OA	Efficacy Safety	10 meloxicam (n = 3351) + 1 Syst Rev 7 etodolac (n = 3411) + 1 Syst Rev	No	4	Narrative review of relationship between NSAID dose, efficacy and safety. Searches to 1997. Included clinical trials in English open label and non-comparative studies. Also evaluated 9 non-selective NSAIDs. Very few of the included trials address the question posed
Garner, 2002 ¹¹⁸	Rofecoxib	RA	Efficacy Safety	2 (n = 8734)	No due to lack of data	7	Review of RCTs with > 50 patients treated for > 4 weeks. Statistical pooling of results planned but not undertaken due to paucity of data
Garner, 2002 (cele) ¹¹²	Celecoxib	RA	Efficacy Safety	5 (n = 4465)	No due to lack of data	6	Review of published RCTs with > 50 patients treated for > 4 weeks. Three studies also included patients with OA. Planned to pool results of studies but data too limited

continued

TABLE 103 Characteristics of included systematic reviews (cont'd)

Review	COX-2 evaluated	Disease population	Outcome domains	Number of trials included (n = patients) ^d	Meta-analysis	Quality score ^b	Comments
Hogue, 2002 ¹²⁷	Celecoxib Rofecoxib	OA	Efficacy Safety	4 celecoxib (n = 9626) + 1 Syst Rev 8 rofecoxib (n > 11,900)	No	2	Narrative review of any studies judged relevant to evaluate the first line treatment options, for OA, specifically paracetamol NSAIDs and COX-2s
Kaplan-Machlis 1999 ¹¹³	Celecoxib Rofecoxib Meloxicam	Any	Efficacy Safety Kinetics Cost	1 celecoxib (n = 330) + manu info 2 rofecoxib (n = 1520) + manu info 10 meloxicam (n = 20,857) + 1 Syst Rev	No	3	Narrative review of the pharmacology of COX-2 selective NSAIDs. Included human clinical, pharmacokinetic and dose ranging trials in Europe and the USA and randomised comparative trials. Data on celecoxib and rofecoxib largely taken from manufacturers' product information since published data were limited in 1999
Luong, 2000 ¹²⁶	Celecoxib	RA	Efficacy, safety, kinetics, cost interactions	4 (n = 3233)	No	3	Narrative review of controlled and uncontrolled trials published in English. Majority of data was referenced as data on file
Mukherjee, 2001 ¹¹⁶	Celecoxib Rofecoxib	Any	Safety (CV events)	1 celecoxib (n = 7968) 3 rofecoxib (n = 10,096)	No	4	Narrative review of English language RCTs. Analysis of MI rates in COX-2 trials (VIGOR and CLASS) vs annualised MI rate in placebo group of recent meta-analysis of 4 aspirin primary prevention trials
NICE, 2000, Addendum, 2001 ¹³⁰	Celecoxib Rofecoxib Meloxicam Etodolac	RA and OA	Efficacy and Safety Cost- effectiveness	77 (n = 61,731) 16 celecoxib (n > 15770) + 1 Syst Rev 15 rofecoxib (n = 16,512) 3 celecoxib and rofecoxib (n = 1374) 13 meloxicam (n = 22,080) 30 etodolac (n = 5352)	Yes but only for AEs	7	Included systematic reviews, RCTs, economic analyses. Original report was updated in Feb. 2001. Narrative of efficacy end-points, data for AEs pooled. Much of the updated data was not available – considered commercially sensitive
Rostom, 2003 ¹²⁵	Celecoxib Rofecoxib Meloxicam	RA, OA or other arthritic condition	Safety – GI	10 celecoxib (n = 28,169) + 1 MA 12 rofecoxib (n = 19,913) + 1 MA 3 celecoxib and rofecoxib (n = 1375) 10 meloxicam (n = 21,421) + 1 MA	Yes	7	Included RCTs and systematic reviews. Evaluated the UGI toxicity of COX-2 with placebo and non-selective NSAIDs ± gastroprotection. Results expressed as RR using fixed-effects model. Sensitivity analysis undertaken to test robustness of results

continued

TABLE 103 Characteristics of included systematic reviews (cont'd)

Review	COX-2 evaluated	Disease population	Outcome domains	Number of trials included (n = patients) ^a	Meta-analysis	Quality score ^b	Comments
Schnitzer, 2001 ¹⁴	Celecoxib Rofecoxib	OA	Efficacy Safety Cost	5 celecoxib (n > 1,000) + 3 Syst Rev + manu info 10 rofecoxib (n > 13,000) + 3 Syst Rev + manu info 1 celecoxib and rofecoxib (n = 382)	No	2	Narrative review on how COX-2 selective NSAIDs may change the management of patients with OA. Types of studies included not specified
Schoenfeld, 1999 ²⁰	Meloxicam	Any	Safety – GI	RA and OA 9 (n > 20,022) + 1 Syst Rev	Yes	3	Included English language RCTs. Pooled analyses presented OR of frequency of events for meloxicam vs NSAIDs. Heterogeneity explored
Symons, 2003 ^{310,450}	Not specified	Not specified	Efficacy Safety Cost- effectiveness	?	?	NA	Included RCTs. Evaluated four strategies for the prevention of NSAID-induced GI toxicity. Insufficient data to evaluate report fully
Towheed, 1997 ²⁸	Etodolac	OA knee	Efficacy	10 etodolac (n = 1090)	No	3	Narrative review of RCTs, single and double blind, and open-label studies, published in English, of drug therapy in knee OA. Difficult to extract meaningful data for etodolac
Vasoo, 2001 ¹¹⁵	Celecoxib Rofecoxib Meloxicam	Any	Efficacy Safety	2 celecoxib (n = 8714) + 1 Syst Rev 3 rofecoxib (n > 1500) + 1 Syst Rev 2 meloxicam (n = 17,979) + 1 Syst Rev	No	2	Narrative review of RCTs, meta-analyses and review articles to provide an update on COX-2 selective NSAIDs
Watson, 2000 ²⁴	Etodolac	OA knee	Efficacy – relative of individual NSAIDs	11 etodolac (n > 1300)	Planned	4	Included RCTs in English. Also evaluated traditional non-aspirin NSAIDs licensed for treatment of OA by GPs Only withdrawal due to lack of efficacy data pooled for etodolac vs diclofenac, naproxen, piroxicam (9 trials)
Weaver, 2001 ¹¹⁷	Rofecoxib	Any	Efficacy Safety	RA and OA 9 (n = 12,365) + 2 reviews	No	2	Narrative review of pharmacology and clinical experience. Type of studies included not specified. Company sponsored

^a MA, meta-analysis; Syst Rev, systematic review.^b On a scale where 1 = extreme flaws to 7 = minimal flaws.

with etodolac 300 mg twice per day compared with 200 mg twice per day, but a second trial found no statistically significant difference between doses.

Celecoxib (see Table 104)

All reviews of celecoxib, except one which did not report efficacy data in OA,¹¹⁵ reported superior efficacy to placebo and comparable efficacy to non-selective NSAIDs in OA and RA.^{112–115,126,127,129,130} Additionally, Schnitzer concluded that celecoxib was superior to paracetamol for OA.¹¹⁴

Etodolac (see Table 105)

The previous HTA report for NICE showed that etodolac was comparable to non-selective NSAIDs including aspirin, piroxicam and ibuprofen in RA; no comparisons with placebo were reported.¹³⁰ In OA, etodolac was more efficacious than placebo,^{124,128,130} and comparable to diclofenac,^{124,128,130} naproxen,^{124,128,130} piroxicam,^{128,130} nimesulide¹³⁰ and tenoxicamin.¹³⁰ Two reviews suggested that etodolac may be more effective than indomethacin¹²⁸ and nabumetone.¹³⁰

Meloxicam (see Table 106)

Two reviews provided data on the efficacy of meloxicam in RA.^{115,130} A third concluded that meloxicam was significantly more effective than placebo and comparable to non-selective NSAIDs.¹¹³ Meloxicam was more efficacious than placebo¹³⁰ and equivalent to diclofenac,^{113,130} piroxicam^{115,130} and naproxen¹¹³ in OA.

Rofecoxib (see Table 107)

Three reviews concluded that rofecoxib was superior to placebo^{117,118,130} and of comparable efficacy to naproxen in RA.^{118,130} In OA, rofecoxib was superior to placebo^{117,127,130} and paracetamol¹¹⁴ and of comparable efficacy to diclofenac,^{113–115,117,127} ibuprofen (high dose),^{113–115,117,127} naproxen¹¹⁴ and nabumetone.¹¹⁷

Valdecoxib (see Table 108)

One review reported that valdecoxib (doses range 10–40 mg/day) was superior to placebo and of comparable efficacy to naproxen in OA and RA.¹¹⁹

Tolerability and safety

All but two reviews^{124,128} evaluated the tolerability and safety of COX-2 selective NSAIDs. Four focused on GI tolerability and safety^{120–122,125} and one on CV safety.¹¹⁶ Safety data, unlike efficacy data, were analysed for all patients irrespective of their disease characteristics.

Twelve studies described tolerability data^{113–119,122,123,126,127,129} and six undertook quantitative analysis.^{53,112,120,121,125,130} Table 109 summarises the pooled estimates calculated in meta-analyses for four key end-points. Pooled estimates as ORs and 95% CIs were shown by two reviews;^{120,130} all other meta-analyses presented summary estimates as RRs with 95% CIs.

Thirteen reviews reported the GI tolerability and safety of celecoxib,^{53,112–116,121,122,125–127,129,130} three of etodolac,^{122,123,130} seven meloxicam,^{113,115,120,122,123,125,130} eleven rofecoxib^{113–118,122,125,127,129,130} and one valdecoxib.³⁶⁸ Rostom and colleagues¹²⁵ described pooled adverse effects for celecoxib, rofecoxib and meloxicam, and for each individual agent.

Data presentation varied greatly in these reviews and three reviews indicated that overall safety of celecoxib,¹¹³ rofecoxib¹¹⁷ and meloxicam¹²³ was comparable to placebo.

Withdrawals due to adverse effects

Compared with placebo

Data for celecoxib (dose range 200–600 mg/day), rofecoxib (12.5–25 mg/day) and meloxicam (7.5 mg/day), where they were reported, showed comparable withdrawal rates to placebo.^{125,130} No data are available for etodolac. Some studies reported more withdrawals with higher doses of COX-2 selective NSAIDs, for example Rostom and colleagues¹²⁵ reported an RR of 1.62 (95% CI 1.16 to 2.25).

Compared with non-selective NSAIDs

Celecoxib,¹¹² etodolac,¹³⁰ meloxicam^{113,130} and rofecoxib¹¹⁸ led to significantly fewer withdrawals from adverse events than non-selective NSAIDs: COX-2 (RR 0.81, 95% CI 0.73 to 0.90),¹²⁵ etodolac (OR 0.44, 95% CI 0.32 to 0.62),¹³⁰ meloxicam (OR 0.80, 95% CI 0.67 to 0.96).¹³⁰

Withdrawals due to GI adverse effects

Compared with placebo

Available data shows that COX-2 selective NSAIDs were comparable to placebo in terms of withdrawals for GI adverse effects: data for COX-2 selective agents combined,¹²⁵ celecoxib 200 mg/day¹³⁰ and rofecoxib.¹¹⁸ However, one review did show an increased incidence of withdrawals for GI adverse effects with celecoxib 400 mg/day compared with placebo (RR 1.71, 95% CI 1.03 to 2.85).¹³⁰ No data are available for etodolac or meloxicam.

TABLE 104 Celecoxib studies in patients with OA or RA included in each systematic review^a

Trial	Kaplan-Machilis, 1999 ¹¹³	Luong, 2000 ¹²⁶	NICE, 2000 ¹³⁰	Ashcroft, 2001 ¹²¹	EI Desoky, 2001 ¹²⁹	Mukherjee, 2001 ¹¹⁶	Schnitzer, 2001 ¹¹⁴	Vasoo, 2001 ¹¹⁵	Deeks, 2002 ⁵³ (cele) ¹¹²	Garner, 2002	Hogue, 2002 ¹²⁷	de Vries, 2002 ¹²²	Rostom, 2003 ¹²⁵	WMHTAC, 2004 ^b
Bensen, 2000 ⁹⁴	✓						✓				✓			* ^c
Bensen, 1999 ^{91,192} Pfizer Study 020	✓						✓		✓		✓			✓
Chan, 2002 ⁵⁹														✓
Clemett, 2000 ³³⁰ Review				✓										* ^b
Emery, 1999 ²¹¹ Pfizer Study 041	✓		✓	✓	✓		✓	✓	✓				✓	✓
Geba, 2002 ²⁸⁵ VACT-1	✓						✓			✓				✓
Gibovsky, 2003 ²⁰² Pfizer Study 003														✓
Goldstein, 2000 ⁹⁵					✓		✓						✓	✓
Goldstein, 2001 ²²⁰ Pfizer Study 062	✓		✓				✓		✓			✓		✓
Goldstein, 2001 ^{195,224} Pfizer Study 096											✓		✓	✓
SUCCESS-1														
Hawel, 2003 ²⁰³														✓
Kivitz, 2001 ¹⁹⁶ Geis 1999b Pfizer study 054	✓	CIC							✓	DOF				✓
Lipsky, 1997 ³³¹														
McKenna, 2001a ¹⁹⁸ Pfizer Study 118	✓	CIC				✓						✓		✓
McKenna, 2001b ¹⁹⁷ Pfizer Study 152	✓										✓			✓
McKenna, 2002 ¹⁹⁹ Pfizer Study 042	✓	CIC												✓

continued

TABLE 104 Celecoxib studies in patients with OA or RA included in each systematic review^a (cont'd)

Trial	Kaplan-Machilis, 1999 ¹¹³	Luong, 2000 ¹²⁶	NICE, 2000/1 ¹³⁰	Ashcroft, 2001 ¹²¹	El Desoky, 2001 ¹²⁹	Mukherjee, 2001 ¹¹⁶	Schnitzer, 2001 ¹¹⁴	Vasoo, 2001 ¹¹⁵	Deeks, 2002 ⁵³	Garner, 2002 (Cele) ¹¹²	Hogue, 2002 ¹²⁷	de Vries, 2002 ¹²²	Rostom, 2003 ¹²⁵	WMHITAC, 2004 ^b
Pfizer Study 021 ²²¹	✓	✓	✓ CIC	✓ FDA									✓ FDA	✓ CIC
Pfizer Study 023 ²²⁷			✓ CIC											✓ CIC
Pfizer Study 047 ⁴⁴			✓ CIC											✓ CIC
Pfizer Study 071 ²²⁶	✓		✓ CIC	✓ FDA				✓ DOF					✓ FDA	✓ CIC
Pfizer Study 105 ⁴⁴⁵														✓ CIC
Pfizer Study 106 ⁴⁴⁶														✓ CIC
Pfizer Study 107 ⁴⁴⁷														✓ CIC
Pfizer Study 209 ⁴³⁹														✓ CIC
Pfizer Study 210 ⁴⁴⁰														✓ CIC
Pfizer Study 211 ²²⁵														✓ CIC
Pfizer Study 216 ²²³														✓ CIC
Pincus, 2003, ²⁰⁵ PACES-a					✓	✓	✓	✓	✓	✓	✓			✓
Pfizer Study 010														
Pincus, 2004, ²⁰⁴ PACES-b														✓
Pfizer Study 249														
Silverstein, 2000 ⁵⁰					✓	✓	✓	✓	✓	✓	✓		✓	✓
Pfizer study 102 -CLASS														
Simon, 1998a ¹⁹⁰	✓		✓ CIC											✓
Pfizer study 012														
Simon, 1998b ¹⁹⁰														✓
Pfizer Study 013														
Simon, 1999 ²¹²														✓
Pfizer study 022		✓	✓ CIC	✓				✓	✓	✓			✓	✓
Sowers, 2003, ^{206,269} CRESCENT														✓ CIC
Pfizer Study 002														

continued

TABLE 104 Celecoxib studies in patients with OA or RA included in each systematic review^a (cont'd)

Trial	Kaplan-Machlis, 1999 ¹¹³	Luong, 2000 ¹²⁶	NICE, 2000 ¹³⁰	Ashcroft, 2001 ¹²¹	El Desoky, 2001 ¹²⁹	Mukherjee, 2001 ¹¹⁶	Schnitzer, 2001 ¹¹⁴	Vasoo, 2001 ¹¹⁵	Deeks, 2002 ⁵³	Garner, 2002 (Cele) ¹¹²	Hogue, 2002 ¹²⁷	de Vries, 2002 ¹²²	Rostom, 2003 ¹²⁵	WMHTAC, 2004 ^b
Suarez-Otero, 2002 ²⁰¹														✓
Whelton, 2001 ²⁸²			✓										✓	✓
SUCCESS VI, Pfizer Study 149													✓	
Whelton, 2002 ²⁸⁴														✓
Pfizer Study 181														
Williams, 2000 ¹⁹⁴			✓										✓	✓
Pfizer Study 060														
Williams, 2001 ²⁰⁰			✓											✓
Pfizer study 087														✓

CIC, commercial-in-confidence; DOF, data on file; FDA, reports available on FDA website.

^a Studies listed are those included in each review to evaluate efficacy and/or safety in patients with RA or OA. Studies in other patient populations are not listed. Reviews/meta-analyses are listed where they formed part of the analysis of efficacy and/or safety. Those referred to just in the introduction or discussion are not listed.

^b This refers to the systematic review presented in the Clinical effectiveness section (Chapter 4) of this monograph.

* Studies excluded due to: ^cpooled analysis; ^dnarrative review.

TABLE 105 Studies with etodolac in patients with RA or OA included in each systematic review^a

Trial	Watson, 2000 ¹²⁴	Towheed, 1997 ¹²⁸	NICE, 2000–1 ¹³⁰	Emery, 2002 ¹²³	de Vries, 2002 ¹²²	WMHTAC, 2004 ^b
Andelman, 1983 ³³²						*a
Astorga Paulsen, 1991 ¹⁴³	✓	✓	✓			✓
Bacon, 1990 ¹³⁶ 6 trials						✓(3) *a
Bianchi Porro, 1991 ^{333,334}			✓			*a
Brasseur, 1991 ¹⁴⁰	×	✓				✓
Briancon, 1991 ³³⁵			✓			*a
BursSENS, 1993 ¹⁴⁹						✓
Chikanza, 1994 ¹⁵¹			✓			✓
Ciampi, 1989 ³³⁶			✓			*b
de Queiros, 1991 ³³⁷			✓			*a
del Toro, 1983 ³³⁸			✓			*a
Delcambre, 1990 ³³⁹						✓
Dick, 1992 ¹⁴⁶	✓	✓	✓			✓
Dick, 1993 ³⁴⁰			✓			*a
Dore, 1995 ¹⁵⁴	✓			✓		✓
Edwards, 1983 ³⁴¹			✓			*a
Eisenkolb, 1993 ¹⁵⁰	✓		✓			✓
Fioravanti, 1989 ³⁴²						*a
Freitas, 1990 ¹³⁹		✓				✓
Gordon, 1983 ³⁴³			✓			*a
Grisanti, 1992 ¹⁴⁷	✓	✓	✓			✓
Jacob, 1983 ³⁴⁴			✓	✓		*a
Jacob, 1985a ³⁴⁵			✓			*a
Jacob, 1985b ³⁴⁶						*a
Jacob, 1986 ³⁴⁷			✓			*a
Jennings, 1997 ¹⁵⁶						✓
Jubb, 1992 ³⁴⁸				✓		*c
Karbowski, 1991 ¹⁴¹	✓	✓				✓
Khan, 1992 ³⁴⁹		✓				*c
Liang, 2003 ³⁵⁰						*a
Lightfoot, 1997 ¹⁶³			✓	✓		✓
Lonauer, 1993 ³⁵¹			✓			*a
Lucker, 1994 ¹⁵²			✓			✓
Neustadt, 1997 ¹⁶⁴			✓	✓		✓
Palferman, 1991 ¹⁴²	✓	✓				✓
Pena, 1991 ¹⁴⁴	✓	✓				✓
Perpignano, 1991 ¹⁴⁵						✓
Perpignano, 1994 ¹⁵³			✓			✓
Porzio, 1993 ³⁵²			✓			*a
Rogind, 1997 ¹⁵⁷			✓			✓
Sanda, 1983 ³⁵³						*a
Schattenkirchner, 1990 ¹⁰⁵				✓		*d
Schattenkirchner, 1991 ³⁵⁴			✓			*a
Schnitzer, 1995 ¹⁵⁵	✓		✓	✓		✓
Schnitzer, 1997 ¹⁵⁸				✓		✓
Taha, 1989 ¹⁵⁹			✓			✓
Taha, 1990 ¹⁶²			✓			✓
Vetter, 1982 ³⁵⁵			✓			*e
Waltham–Weeks, 1987 ³⁵⁶			✓			*a
Waterworth, 1992 ¹⁴⁸	✓					✓
Williams, 1989 ¹³⁸		✓	✓			✓

^a Studies listed are those included in each review to evaluate efficacy and/or safety in patients with RA or OA. Studies in other patient populations are not listed. Reviews/meta-analyses are listed where they formed part of the analysis of efficacy and/or safety. Those referred to just in the introduction or discussion are not listed.

^b This refers to the systematic review presented in the Clinical effectiveness section (Chapter 4).

* Studies excluded due to: ^asub-licensed doses; ^bduration of treatment less than 2 weeks; ^cinterim trial reports; ^dpooled analysis; ^einappropriate design.

TABLE 106 Studies with meloxicam in patients with RA or OA included in each systematic review^a

Trial	Kaplan–Machlis B, 1999 ¹¹³	Schoenfeld, 1999 ¹²⁰	NICE, 2000–1 ¹³⁰	Vasoo, 2001 ¹¹⁵	Emery, 2002 ¹²³	de Vries, 2002 ¹²²	Rostom, 2003 ¹²⁵	WMHTAC, 2004 ^b
Carrabba, 1995 ¹⁶⁸		✓			✓			✓
Chang, 2001 ¹⁷⁹						✓		✓
Dequeker, 1998 ¹⁷² SELECT, BI Study 154	✓	✓	✓	✓			✓	✓
Distel, 1996 ^{96,104}	✓	✓			✓		✓	* ^b
Furst, 2002, ¹⁶⁷ BI Study 183								✓
Ghozlan, 1996 ³⁵⁷	✓				✓			* ^c
Goei The, 1997 ¹⁶⁶ BI Study 044	✓	✓	✓				✓	✓
Hawkey, 1998 ¹⁷³ MELISSA, BI Study 153	✓	✓	✓	✓			✓	✓
Hettich, 1997 ³⁵⁸ BI Study 099			✓					* ^a
Hosie, 1996 ¹⁷⁰ BI Study 063	✓	✓	✓		✓		✓	✓
Hosie, 1997 ¹⁷¹ BI Study 045	✓	✓	✓		✓		✓	✓
Hsu, 1999 ³⁵⁹ BI Study 196			✓					* ^a
Huskisson, 1996 ³⁶⁰					✓			* ^d
Lemmel, 1997 ^{184,185} BI Study 035	✓		✓		✓		✓	✓
Linden, 1996 ¹⁶⁵ BI Study 043	✓	✓	✓		✓		✓	✓
Lipscomb, 1998 ³⁶¹		✓						* ^e
Lund, 1998 ¹⁷⁴ BI Study 042	✓		✓				✓	✓
Prouse, 1996 ³⁶²					✓			* ^d
Reginster, 1996 ³⁶³					✓			* ^f
Valat, 2001 ¹⁸⁰ BI Study 094			✓			✓		✓
Wojtulewski, 1996 ^{182,183} BI Study 61	✓	✓	✓		✓		✓	✓
Xu, 2002a ¹⁸⁷								✓
Xu, 2002b ¹⁸¹								✓
Yocum, 2000 ¹⁷⁶ BI Study 181			✓			✓	✓	✓

BI, Boehringer Ingelheim.

^a Studies listed are those included in each review to evaluate efficacy and/or safety in patients with RA or OA. Studies in other patient populations are not listed. Reviews/meta-analyses are listed where they formed part of the analysis of efficacy and/or safety. Those referred to just in the introduction or discussion are not listed.

^b This refers to the systematic review presented in the Clinical effectiveness section (Chapter 4).

* Studies excluded due to: ^aonly abstract available; ^bpooled analysis; ^cduration of treatment less than 2 weeks; ^ddescriptive study without control group; ^ehealthy volunteer; ^fcomparing different doses without other active or placebo control.

TABLE 107 Studies with rofecoxib in patients with RA or OA included in each systematic review^a

Trial	Kaplan-Machlis, 1999 ¹¹³	NICE, 2000-1 ¹³⁰	Desoky, 2001 ¹²⁹	Mukherjee, 2001 ¹¹⁶	Schnitzer, 2001 ¹¹⁴	Vasoo, 2001 ¹¹⁵	Weaver, 2001 ¹¹⁷	Garner, 2002 ¹¹⁸	Hogue, 2002 ¹²⁷	de Vries, 2002 ¹²²	Rostom, 2003 ¹²⁵	WMHTAC, 2004 ^b
Acevedo, 2001 ²³⁶		✓								✓	✓	✓
Arthrotec trial, MSD Study 902												
Bombardier, 2000 ⁶⁶ VIGOR Study		✓ + CIC		✓ + FDA 2001	✓	Pre-publication	✓	✓	✓		✓	✓
Cannon, 2000 ²³⁰	✓	✓			✓	✓	✓		✓		✓	✓
MSD Study 035												
Day, 2000 ²³²		✓			✓	✓	✓		✓		✓	✓
MSD Study 040												
Ehrich, 1999 ²²⁹		✓			✓		✓				✓	✓
MSD Study 010												
Ehrich, 2001 ²³⁷		✓			✓		✓					✓
MSD Study 029												
Geba, 2001 ³⁶⁴				✓ 2001								✓
MSD Study 090												
Geba, 2002 ²⁸⁵		✓			✓				✓		✓	✓
VACT-1 Study												
Geusens, 2002 ²⁴⁷												✓
MSD Study 097												
Gibofsky, 2003 ²⁰²												✓
Pfizer Study 003												
Hawkey, 2000 ²³⁴		✓							✓		✓	✓
MSD Study 044 /045												
Hawkey, 2003 ²⁴⁸												✓
MSD Study 098/103												
Kivitz, 2004 ¹⁶¹		✓		✓ 2001								✓
MSD Study 085												
Laine, 1999 ³⁷		✓			✓		✓		✓		✓	✓
MSD Study 044/045												
Langman, 1999 ³²					✓	✓	✓				✓	*a

continued

TABLE 107 Studies with rofecoxib in patients with RA or OA included in each systematic review^a (cont'd)

Trial	Kaplan-Machlis, 1999 ¹¹³	NICE, 2000-1 ¹³⁰	Desoky, 2001 ¹²⁹	Mukherjee, 2001 ¹¹⁶	Schnitzer, 2001 ¹¹⁴	Vasoo, 2001 ¹¹⁵	Weaver, 2001 ¹¹⁷	Garner, 2002 ¹¹⁸	Hogue, 2002 ¹²⁷	de Vries, 2002 ¹²²	Rostom, 2003 ¹²⁵	WMHTAC, 2004 ^b
Lanza, 1999 ³⁶⁵					✓				✓			*b
Lisse, 2003 ²⁴⁴											✓	✓
ADVANTAGE											✓	Geba, 2001 ^c
MSD Study 102/903												
McKenna, 2001b ¹⁹⁷		✓							✓		✓	✓
Pfizer Study 152												
Moskowitz, 2003 ^{245,286}												✓
Pfizer Study 143												
Myllykangas-Luosujärvi, 2002 ²⁴³												✓
MSD Study 901												
Niccoli, 2002 ²²⁸												✓
Saag, 2000a ^{235,366}	✓		✓		✓		✓		✓		✓	✓
MSD Study 033												
Saag, 2000b ²³⁵			✓		✓						✓	✓
MSD Study 034												
Schnitzer, 1999 ²⁴⁶			✓		✓		✓	✓			✓	✓
MSD Study 068												
Sowers, 2003 ²⁰⁶												✓ CIC
CRESCENT												
Pfizer Study 002												
Truitt, 2001 ²⁴²							✓				✓	✓
MSD Study 058												
Truitt, 2001 ³⁶⁷												✓
MSD Study 096												
Whelton, 2001 ²⁸²												✓
SUCCESS VI,												
Pfizer Study 149											✓	✓
Whelton, 2002a ²⁸⁴												✓
SUCCESS VII												
Pfizer Study 181												

continued

TABLE 107 Studies with rofecoxib in patients with RA or OA included in each systematic review^a (cont'd)

Trial	Kaplan-Machlis, 1999 ¹¹³	NICE, 2000-1 ¹³⁰	Desoky, 2001 ¹²⁹	Mukherjee, 2001 ¹¹⁶	Schnitzer, 2001 ¹¹⁴	Vasoo, 2001 ¹¹⁵	Weaver, 2001 ¹¹⁷	Garner, 2002 ¹¹⁸	Hogue, 2002 ¹²⁷	de Vries, 2002 ¹²²	Rostom, 2003 ¹²⁵	WMHTAC, 2004 ^b
Daniels, Krupa, 1999 ⁴⁵² (abstract)				✓	✓		✓					
Daniels, Seidenberg, 1999 ⁴⁵³ (abstract) review				✓	✓							
Daniels, Gertz, 1999 ⁴⁵⁴ (abstract) review					✓		✓					
Laurenzi, 2000a ⁴⁵⁵ (abstract)		✓										

CIC, commercial-in-confidence.
^a Studies listed are those included in each review to evaluate efficacy and/or safety in patients with RA or OA. Studies in other patient populations are not listed. Reviews/meta-analyses are listed where they formed part of the analysis of efficacy and/or safety. Those referred to just in the introduction or discussion are not listed.
^b This refers to the systematic review presented in the Clinical effectiveness section (Chapter 4).
^c This abstract (Geba, 2001⁴⁵¹) rather than Lisse, 2003²⁴⁴ was cited in the review by Rostom and colleagues.
^{*} Studies excluded due to: ^a pooled analysis; ^b healthy volunteer.

TABLE 108 Studies with valdecoxib in patients with RA or OA included in each systematic review^a

Trial	Chavez, 2003 ¹¹⁹	WMHTAC, 2004 ^b
Bensen, 2002 ²⁶⁴ Pfizer Study 060	✓	✓
Fiechtner, 2001 ^{258,268} Pfizer Study 015	✓	✓
Kivitz, 2002 ²⁵⁹ Pfizer Study 053	✓	✓
Makarowski, 2002 ²⁶⁰ Pfizer Study 049	✓	✓
Moskowitz, 2003 ^{245,286} Pfizer Study 143		✓
Pavelka, 2003 ²⁶⁵ Pfizer Study 062		✓
Sikes, 2002 ²⁶¹ Pfizer Study 048	✓	✓
Pfizer Study 016		✓ CIC
Pfizer Study 047		✓ CIC
Pfizer Study 061		✓ CIC
Pfizer Study 063		✓ CIC
Agrawal, 2001 ⁴⁵⁶ (abstract)	✓	
Goldstein, 2001 ⁴⁵⁷ (abstract)	✓	
Goldstein, 2002a ⁴⁵⁸ (abstract)	✓	
Goldstein, 2002b ⁴⁵⁹ (abstract)	✓	

CIC, commercial-in-confidence.

^a Studies listed are those included in each review to evaluate efficacy and/or safety in patients with RA or OA. Studies in other patient populations are not listed. Reviews/meta-analyses are listed where they formed part of the analysis of efficacy and/or safety. Those referred to just in the introduction or discussion are not listed.

^b This refers to the systematic review presented in the Clinical effectiveness section (Chapter 4).

Compared with non-selective NSAIDs

A majority of reviews consistently showed that COX-2 selective NSAIDs significantly reduced the incidence of GI adverse events compared with non-selective NSAIDs:^{112–115,120,125,130} RR: 0.73 (95% CI 0.69 to 0.79) for COX-2 selective NSAIDs combined,¹²⁵ RR 0.4 (95% CI 0.2 to 0.8) for celecoxib 400 mg/day compared with ibuprofen,¹³⁰ and OR 0.59 (95% CI 0.52 to 0.67) for meloxicam.¹²⁰ No significant differences were apparent on comparing etodolac with piroxicam¹³⁰ (Table 109).

Ulcer on endoscopy

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

Compared with placebo

Few comparisons of COX-2 selective NSAIDs with placebo are reported. Compared with placebo, the incidence of ulcers on endoscopy is not significantly different for COX-2 selective NSAIDs combined,¹²⁵ celecoxib,^{112,114} rofecoxib^{113,114,117} and valdecoxib.¹¹⁹ One review¹²¹ reported that celecoxib at 400 mg/day, but not 200 mg/day,

significantly increased the risk of endoscopic ulcers, compared with placebo (RR 2.35, 95% CI 1.02 to 5.38).

Compared with non-selective NSAIDs

Reviews consistently showed that COX-2 selective NSAIDs reduced the incidence of ulcers on endoscopy compared with non-selective NSAIDs. For selective NSAIDs combined, a 73% reduction in risk was reported (RR 0.27; 95% CI 0.23 to 0.32).¹²⁵ Details for individual NSAIDs are given below.

Celecoxib

Compared with naproxen 1 g/day and ibuprofen 2.4 g/day, celecoxib caused fewer endoscopic ulcers over the short term.^{112–115,127} A statistically significant reduction in ulcer incidence compared with diclofenac was seen at 6 months but not 3 months.^{112,113,115,127} Celecoxib (100–800 mg/day)^{112,121,125} reduced the risk of endoscopic ulcers by 70–80%.^{112,121,125} In a stratified analysis, Rostom and colleagues¹²⁵ showed significant benefits for celecoxib compared with naproxen and ibuprofen, but not diclofenac.¹²⁵

Rofecoxib

Significantly fewer endoscopic ulcers were reported for rofecoxib compared with ibuprofen over the short term and combined non-selective NSAIDs^{113,114,117} (RR 0.25; 95% CI 0.20 to 0.32).¹²⁵

Valdecoxib

Limited data are available for valdecoxib:¹¹⁹ after 12 weeks, valdecoxib 20 mg/day had a similar incidence of gastroduodenal ulcers on endoscopy compared with naproxen 1 g/day, ibuprofen 2.4 g/day and diclofenac 150 mg/day.

Upper GI perforations, ulcers and bleeding (PUB)

Reviews differed in their definition of PUB; for example, the HTA report for NICE defined PUBs as 'Perforations, ulcers and bleeding assessed clinically or endoscopically',¹³⁰ and Schoenfeld and colleagues as gastric perforations, endoscopically diagnosed ulcers in patients with dyspepsia or abdominal pain and/or GI bleeding.¹²⁰

Compared with placebo

Data are very limited and previous reports may give inaccurate estimates of risk because of incomplete study inclusions. The previous NICE HTA review found no significant differences between celecoxib and placebo (OR 1.83, 95% CI 0.88 to 3.83) and a significant increase in PUBs for rofecoxib versus placebo (OR 2.25, 95% CI 1.12 to 4.50).

Compared with non-selective NSAIDs

Rostom and colleagues¹²⁵ reported a 51% reduction in PUBs for COX-2 selective NSAIDs (celecoxib, rofecoxib, meloxicam) compared with non-selective NSAIDs (diclofenac, ibuprofen, naproxen or piroxicam): RR 0.49, 95% CI 0.41 to 0.60. Analysis for individual non-selective NSAIDs showed that a significant reduction in risk did not apply to diclofenac. A single trial comparing piroxicam with meloxicam did not show any difference in PUB rates.¹²⁵ Details for individual COX-2 selective agents are given below.

Celecoxib

Celecoxib significantly reduced the risk of PUBs compared with non-selective NSAIDs^{125,130} (see *Table 109*) and preliminary analysis found that this benefit was lost when low-dose aspirin was given with celecoxib.

Etodolac

Etodolac did not cause significantly fewer PUBs compared with non-selective NSAIDs in a long-term RCT.¹²² However, the previous HTA report for NICE, which included this study, suggested significant benefits for etodolac (clinical and endoscopic PUBs: OR 0.20, 95% CI 0.07 to 0.53) compared with non-selective NSAIDs.

Meloxicam

Few events occurred in meloxicam trials but two reviews found no difference in the incidence of PUBs between piroxicam, diclofenac or meloxicam.^{113,115} Other studies, reporting pooled data, indicated significant benefits for meloxicam with approximately a 50% reduction in risk (*Table 109*); however, these reviews included studies that defined PUBs less precisely.^{120,125,130}

Rofecoxib

Reviews concluded that PUBs were significantly reduced with rofecoxib compared with diclofenac, ibuprofen, nabumetone and naproxen over the short term,^{114,117,118} but de Vries and colleagues¹²² found, in an RCT, that over 1 year rofecoxib and diclofenac did not differ significantly. Pooled analyses indicated a significantly reduced risk of PUBs with rofecoxib 12.5–50 mg/day compared with non-selective NSAIDs^{125,130} (refer to *Table 109*).

Other adverse events**Renal**

Abnormalities of renal function were evaluated in six reviews, which found that COX-2 selective and non-selective NSAIDs had similar effects on the kidney function,^{114,115,117,118} although insufficient data were available for meloxicam¹¹³ and valdecoxib.¹¹⁹

Cardiovascular

Mukherjee and colleagues¹¹⁶ looked specifically at the CV safety of COX-2 selective NSAIDs. They reported on four trials: two small studies, VIGOR and CLASS. Annualised MI rates from VIGOR and CLASS were compared with the rate in the placebo group of a large meta-analysis of patients in primary prevention trials (0.74 and 0.80 versus 0.52; $p < 0.05$ for both versus placebo). There are obvious concerns about such indirect comparisons, especially as patients with RA have a higher risk of CV disease and also because of potential differences in the anti-platelet actions of non-selective NSAIDs. One review of valdecoxib found too few events to draw any conclusions.¹¹⁹

TABLE 109 Summary estimates presented in quantitative reviews on COX-2 selective NSAIDs – GI tolerability and safety outcomes

Drug dose/time point (where specified)	Review ^d	Comparison	Withdrawals due to AEs	95% CI	Withdrawals due to any GI AE	95% CI	Ulcer on endoscopy	95% CI	Clinical PUBs	95% CI	Comment
COX 2											
COX-2 low dose ^b	Rostom, 2003 ¹²⁵	Placebo	RR 1.13	0.91 to 1.40 13 trials n = 6311							
COX-2 high dose ^b	Rostom, 2003 ¹²⁵	Placebo	RR 1.62	1.16 to 2.25 6 trials n = 1863							
COX-2 all doses	Rostom, 2003 ¹²⁵	Placebo			RR 1.35	0.83 to 2.20 8 trials n = 4478	RR 1.09	0.74 to 1.60 4 trials n = 2576			
COX-2 all doses	Rostom, 2003 ¹²⁵	NSAID	RR 0.81	0.73 to 0.90 22 trials n = 44,840	RR 0.73	0.69 to 0.79 15 trials n = 49,706	RR 0.27	0.23 to 0.32 7 trials n = 4677	RR 0.49	0.41 to 0.60 7 trials n = 61,282	PUB and endoscopic ulcers stratified by comparator NSAID. Statistically significant difference seen vs naproxen and ibuprofen but not diclofenac
Celecoxib											
Celecoxib 200 mg/day, 12 weeks	Ashcroft, 2001 ¹²¹	Placebo					RR 1.96	0.85 to 4.55 2 trials n = 953			The individual trials found no dose-related increase in endoscopic ulcers with celecoxib 100–800 mg/day over 12 weeks
Celecoxib 400 mg/day, 12 weeks	Ashcroft, 2001 ¹²¹	Placebo					RR 2.35 ^b	1.02 to 5.38 2 trials n = 941			
Celecoxib 200–600 mg/day	NICE HTA, 2000–1 ¹³⁰	Placebo	OR 0.89	0.45 to 1.77 3 trials n = 2210					Endoscopic OR 1.83	0.88 to 3.83 2 trials n = 1421	
Celecoxib 200 mg/day, 12 weeks	NICE HTA, 2000–1 ¹³⁰	Placebo			RR 1.67	1.0 to 2.79 ? trials n = ?					No other statistically significant difference in GI withdrawals seen at other doses and time points but numerical data not presented
Celecoxib 400 mg/day, 12 weeks	NICE HTA, 2000–1 ¹³⁰	Placebo			RR 1.71 ^b	1.03 to 2.85 ? trials n = ?					

continued

TABLE 109 Summary estimates presented in quantitative reviews on COX-2 selective NSAIDs – GI tolerability and safety outcomes (cont'd)

Drug dose/time point (where specified)	Review ^a	Comparison	Withdrawals due to AEs	95% CI	Withdrawals due to any GI AE	95% CI	Ulcer on endoscopy	95% CI	Clinical PUBs	95% CI	Comment
Celecoxib 50–800 mg/day (incl. 12 month CLASS data)	Rostom, 2003 ¹²⁵	NSAIDs					RR 0.28	0.23 to 0.35 5 trials n = 3590	RR 0.43	0.21 to 0.88 3 trials n = 30306	When analysed by comparator NSAID, celecoxib vs diclofenac not significant for endoscopic ulcers
Celecoxib 200–800 mg/day	NICE HTA, 2000–1 ¹³⁰	NSAIDs	OR 0.84	0.46 to 1.52 4 trials n = 10137					Endoscopic OR 0.28	0.09 to 0.92 3 trials n = 9101	
Celecoxib 200 mg/day, 12 weeks	Ashcroft, 2001 ¹²¹	Naproxen 1000 mg/day					RR 0.22	0.13 to 0.37 2 trials n = 931			NNH = 9 for ulcer on endoscopy
Celecoxib 400 mg/day, 12 weeks	Ashcroft, 2001 ¹²¹	Naproxen 1000 mg/day					RR 0.24	0.17 to 0.33 3 trials n = 1456			NNH = 7 for ulcer on endoscopy
Celecoxib 400 mg/day	Garner, 2002 ¹¹²	Naproxen 1000 mg/day					RR 0.2	0.11 to 0.38 2 trials n = 398			
Celecoxib 400 mg/day	NICE HTA, 2000–1 ¹³⁰	Ibuprofen					RR 0.40	0.20 to 0.80			Not referenced, 1 study
Etodolac											
Etodolac 100–1000 mg/day	NICE HTA, 2000–1 ¹³⁰	NSAID	OR 0.44 ^b	0.32 to 0.62 6 trials n = 1259					Endoscopic OR 0.20	0.07 to 0.53 4 trials n = 1410	No pooling vs placebo
Etodolac 600 mg/day, 6 weeks	NICE HTA, 2000–1 ¹³⁰	Diclofenac 150 mg/day					RR 0.89	0.31 to 2.58 2 trials n = 307			
Etodolac 600 mg/day, 8 weeks	NICE HTA, 2000–1 ¹³⁰	Piroxicam 20 mg/day	RR 0.80	0.49 to 1.32 2 trials n = 491			RR 0.74	0.41 to 1.36 2 trials n = 491			
Meloxicam											
Meloxicam 7.5–15 mg/day	NICE HTA, 2000–1 ¹³⁰	Placebo	OR 0.84	0.45 to 1.55 2 trials n = 879							

continued

TABLE 109 Summary estimates presented in quantitative reviews on COX-2 selective NSAIDs – GI tolerability and safety outcomes (cont'd)

Drug dose/time point (where specified)	Review ^a	Comparison	Withdrawals due to AEs	95% CI	Withdrawals due to any GI AE	95% CI	Ulcer on endoscopy	95% CI	Clinical PUBs	95% CI	Comment
Meloxicam 7.5–15 mg/day	Schoenfeld, 1999 ¹²⁰	NSAIDs			OR 0.59 ^b	0.52 to 0.67 7 trials n = 19,442			Endoscopic OR 0.52	0.28 to 0.96 6 trials n = 19,331	
Meloxicam 7.5 mg/day	Rostom, 2003 ¹²⁵	NSAIDs							RR 0.53	0.26 to 1.05 2 trials n = 17,979	When 6 efficacy trials added to the analysis, RR for PUB 0.48, 95% CI 0.26 to 0.88
Meloxicam 7.5–15 mg/day	NICE HTA, 2000– ¹³⁰	NSAIDs	OR 0.80	0.67 to 0.96 8 trials n = 19,892					Endoscopic OR 0.49	0.26 to 0.91 7 trials n = 19,663	
Rofecoxib											
Rofecoxib 12.5–50 mg	NICE HTA, 2000– ¹³⁰	Placebo	OR 1.74	1.03 to 2.94 4 trials n = 1861					Endoscopic OR 2.25	1.12 to 4.50 3 trials n = 1301	
Rofecoxib 12.5 mg/day, 6–8 weeks	NICE HTA, 2000– ¹³⁰	Placebo	RR 1.38	0.81 to 2.36 4 trials n = 1527							
Rofecoxib 25 mg/day, 6–8 weeks	NICE HTA, 2000– ¹³⁰	Placebo	RR 1.15	0.67 to 2.00 5 trials n = 1378							
Rofecoxib 50 mg/day, 6–8 weeks	NICE HTA, 2000– ¹³⁰	Placebo	RR 1.95	0.90 to 4.26 2 trials n = 571							
Rofecoxib 25 mg/day, 18–24 weeks	NICE HTA, 2000– ¹³⁰	Placebo	RR 1.21	0.69 to 2.11 2 trials n = 733							
Rofecoxib 50 mg/day 18–24 weeks	NICE HTA, 2000– ¹³⁰	Placebo	RR 1.87 ^b	1.12 to 3.12 2 trials n = 723							
Rofecoxib 25–50 mg/day	Rostom, 2003 ¹²⁵	NSAIDs					RR 0.25	0.20 to 0.32 2 trials n = 1087	RR 0.47	0.36 to 0.63 2 trials n = 12,997	

continued

TABLE 109 Summary estimates presented in quantitative reviews on COX-2 selective NSAIDs – GI tolerability and safety outcomes (cont'd)

Drug dose/time point (where specified)	Review ^a	Comparison	Withdrawals due to AEs	95% CI	Withdrawals due to any GI AE	95% CI	Ulcer on endoscopy	95% CI	Clinical PUBs	95% CI	Comment
Rofecoxib 12.5–50 mg/day	NICE HTA, 2000–1 ³⁰	NSAIDs	OR 0.81	0.54 to 1.20 3 trials n = 9595					OR 0.29 ^b	0.12 to 0.72 4 trials n = 10176	
Rofecoxib 12.5 mg/day, 1 year	NICE HTA, 2000–1 ³⁰	Diclofenac	RR 0.68	0.36 to 1.30 2 trials n = 988	RR 0.47	0.22 to 1.02 ? trials n = ?					
Rofecoxib 25 mg/day, 1 year	NICE HTA, 2000–1 ³⁰	Diclofenac	RR 0.70 ^b	0.50 to 0.97 2 trials n = 987	RR 0.63	0.31 to 1.26 ? trials n = ?					
Rofecoxib 12.5 mg/day, 6 weeks	NICE HTA, 2000–1 ³⁰	Ibuprofen	RR 0.74	0.44 to 1.27 ? trials n = ?							
Rofecoxib 25 mg/day, 6 weeks	NICE HTA, 2000–1 ³⁰	Ibuprofen	RR 0.80	0.47 to 1.36 ? trials n = ?							
Rofecoxib 25 mg/day, 24 weeks	NICE HTA, 2000–1 ³⁰	Ibuprofen	RR 0.61 ^b	0.39 to 0.97 ? trials n = ?							
Rofecoxib 50 mg/day, 24 weeks	NICE HTA, 2000–1 ³⁰	Ibuprofen	RR 0.94	0.62 to 1.42 ? trials n = ?							

AEs, adverse events; GI AEs, gastrointestinal adverse events; PUBs, perforations, ulcers and bleeds. Results from meta-analyses of placebo-controlled trials were shaded to reflect the focus on benefits and harms of COX-2 selective NSAIDs relative to non-selective NSAIDs in this monograph. Statistically significant results were shown in *italic* in the table.

^a For all quantitative reviews only comparisons where data from more than one trial are pooled are presented. Results from single trials are not included. Data from the NICE HTA for some comparisons are limited since forest plots have been removed due to commercially sensitive status – only limited data are presented in the text.

^b Low-dose COX-2 was defined as celecoxib 200 mg twice daily or less, rofecoxib 25 mg daily or less and meloxicam 7.5 mg daily. High-dose COX-2 was defined as celecoxib 400 mg twice daily, rofecoxib 50 mg daily and meloxicam 15 mg daily.

Appendix 2

Search strategies

Clinical effectiveness – systematic reviews/meta-analyses

Cochrane Library

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

ARIF Database

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

NHSCRD (Internet access)

- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews.

Health Technology Assessments (Internet access)

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

Clinical evidence

Bandolier (via the Internet)

National Research Register

TRIP Database

Drug and Therapeutics Bulletin (where appropriate)

Bibliographic databases

- MEDLINE – systematic reviews
- EMBASE – systematic reviews
- Other specialist databases.

Contacts

- Cochrane Collaboration (via Cochrane Library)
- regional experts, especially Pharmacy Prescribing Unit, Keele University (and Midlands Therapeutics Review and Advisory Committee) and West Midlands Drug Information Service (URL: www.ukmicentral.nhs.uk) for any enquiry involving drug products
- Scottish Intercollegiate Guidelines Network (SIGN). (Web page, newsletter and personal contact)
- in special circumstances, Mailbase discussion lists, e.g. Evidence Based Medicine.

Clinical effectiveness – trials

Cochrane Library (CENTRAL) Issue 4 2003

(etoricoxib OR arcoxia OR mk-663 OR mk-0663)
(valdecoxib OR bextra)
(lumiracoxib OR prexige)
(cyclooxygenase*)
(cyclo oxygenase*)
cox*
cyclo oxygenase inhibitors: ME
arthritis* OR osteoarthritis*
arthritis:ME

MEDLINE (Ovid) 1966 to October Week 5 2003

- 1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (39)
- 2 (valdecoxib or bextra).mp. (78)
- 3 (lumiracoxib or prexige).mp. (5)
- 4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6244)
- 5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (435)
- 6 (cox-2 or cox2 or cox-II or coxII).mp. (5577)
- 7 cyclooxygenase inhibitors/ (8907)
- 8 (arthritis\$ or osteoarthritis\$).mp. (111948)

- 9 exp arthritis/ (120165)
- 10 or/1-7 (13236)
- 11 or/8-9 (135062)
- 12 10 and 11 (1158)
- 13 randomized controlled trial.pt. (184388)
- 14 controlled clinical trial.pt. (65285)
- 15 randomized controlled trials/ (31418)
- 16 random allocation/ (49965)
- 17 double blind method/ (76989)
- 18 single blind method/ (7727)
- 19 or/13-18 (312525)
- 20 (animal not human).sh. (2727877)
- 21 19 not 20 (297146)
- 22 clinical trial.pt. (373560)
- 23 exp clinical trials/ (152583)
- 24 (clin\$ adj25 trial\$).ti,ab. (96466)
- 25 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab. (76132)
- 26 placebos/ (23379)
- 27 placebo\$.ti,ab. (82499)
- 28 random\$.ti,ab. (275581)
- 29 research design/ (38586)
- 30 or/22-29 (655011)
- 31 30 not 20 (609528)
- 32 31 not 21 (322306)
- 33 comparative study/ (1080263)
- 34 exp evaluation studies/ (475771)
- 35 follow up studies/ (276271)
- 36 prospective studies/ (168637)
- 37 (control\$ or prospectiv\$ or volunteer\$).ti,ab. (1387557)
- 38 or/33-37 (2786860)
- 39 38 not 20 (2135191)
- 40 38 not (21 or 32) (2360488)
- 41 21 or 32 or 40 (2979940)
- 42 12 and 41 (530)

EMBASE (Ovid) 1980 to 2003 Week 45

- 1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (144)
- 2 (valdecoxib or bextra).mp. (250)
- 3 (lumiracoxib or prexige).mp. (37)
- 4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (5915)
- 5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (426)
- 6 (cox-2 or cox2 or cox-II or coxII).mp. (5317)
- 7 exp cyclooxygenase 2 inhibitor/ (7646)
- 8 exp cyclooxygenase 2/ (4854)
- 9 or/1-8 (11554)
- 10 (arthrit\$ or osteoarthrit\$).mp. (72344)
- 11 exp arthritis/ (88712)
- 12 or/10-11 (100290)
- 13 9 and 12 (2092)
- 14 randomized controlled trial/ (79774)
- 15 exp clinical trial/ (288658)

- 16 exp controlled study/ (1659851)
- 17 double blind procedure/ (49843)
- 18 randomization/ (8060)
- 19 placebo/ (66349)
- 20 single blind procedure/ (4462)
- 21 (control\$ adj (trial\$ or stud\$ or evaluation\$ or experiment\$)).mp. (102121)
- 22 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).mp. (69385)
- 23 (placebo\$ or matched communities or matched schools or matched populations).mp. (107912)
- 24 (comparison group\$ or control group\$).mp. (104120)
- 25 (clinical trial\$ or random\$).mp. (475502)
- 26 (quasiexperimental or quasi experimental or pseudo experimental).mp. (928)
- 27 matched pairs.mp. (1489)
- 28 or/14-27 (1998877)
- 29 13 and 28 (1181)

MEDLINE In-process and Other Non-indexed Citations (Ovid) 11 November 2003

- 1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (11)
- 2 (valdecoxib or bextra).mp. (12)
- 3 (lumiracoxib or prexige).mp. (5)
- 4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (330)
- 5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (25)
- 6 (cox-2 or cox2 or cox-II or coxII).mp. (513)
- 7 cyclooxygenase inhibitor\$.mp. (53)
- 8 or/1-7 (676)
- 9 (arthrit\$ or osteoarthrit\$).mp. (1770)
- 10 8 and 9 (50)

Cochrane Library (CENTRAL) Issue 4 2003

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

MEDLINE (Ovid) 1966 to October Week 4 2003

- 1 (celecoxib or celebrex or sc-58635).mp. (977)
- 2 (rofecoxib or vioxx or mk-0966).mp. (721)
- 3 (etodolac or lodine or ultradol).mp. (311)

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

EMBASE (Ovid) 1980 to 2003 Week 44

- 1 (celecoxib or celebrex or sc-58635).mp. (2641)
- 2 (rofecoxib or vioxx or mk-0966).mp. (2069)
- 3 (etodolac or lodine or ultradol).mp. (1075)
- 4 (meloxicam or mobic).mp. (1060)
- 5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (5872)
- 6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (422)
- 7 (cox-2 or cox2 or cox-II or coxII).mp. (5269)

- 8 exp Cyclooxygenase 2 Inhibitor/ (7565)
- 9 exp Cyclooxygenase 2/ (4819)
- 10 or/1-9 (12193)
- 11 (arthrit\$ or osteoarthrit\$).mp. (72193)
- 12 exp arthritis/ (88525)
- 13 or/11-12 (100085)
- 14 10 and 13 (2357)
- 15 randomized controlled trial/ (79570)
- 16 exp clinical trial/ (287950)
- 17 exp controlled study/ (1655846)
- 18 double blind procedure/ (49755)
- 19 randomization/ (7964)
- 20 placebo/ (66226)
- 21 single blind procedure/ (4448)
- 22 (control\$ adj (trial\$ or stud\$ or evaluation\$ or experiment\$)).mp. (101782)
- 23 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).mp. (69294)
- 24 (placebo\$ or matched communities or matched schools or matched populations).mp. (107723)
- 25 (comparison group\$ or control group\$).mp. (103953)
- 26 (clinical trial\$ or random\$).mp. (474493)
- 27 (quasiexperimental or quasi experimental or pseudo experimental).mp. (927)
- 28 matched pairs.mp. (1489)
- 29 or/15-28 (1994308)
- 30 14 and 29 (1313)

MEDLINE In-process and Other Non-indexed Citations (Ovid) 4 November 2003

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

Economic evaluation/decision analysis

MEDLINE (Ovid) 1966 to November Week 2 2003

- 1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (40)

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

EMBASE (Ovid) 1980 to 2004 Week 4

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

Ovid MEDLINE In-process and Other Non-indexed Citations (Ovid) 22 January 2004

- 1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (10)
- 2 (valdecoxib or bextra).mp. (12)
- 3 (lumiracoxib or prexige).mp. (6)
- 4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (320)

- 5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (33)
- 6 (cox-2 or cox2 or cox-II or coxII).mp. (527)
- 7 cyclooxygenase inhibitor\$.mp. (57)
- 8 or/1-7 (689)
- 9 markov.mp. (249)
- 10 model\$.mp. (35510)
- 11 decision analysis.mp. (40)
- 12 cost benefit analysis.mp. (31)
- 13 or/9-12 (35620)
- 14 8 and 13 (114)

MEDLINE (Ovid) 1966 to January 2004

- 1 (celecoxib or celebrex or sc-58635).mp. (942)
- 2 (rofecoxib or vioxx or mk-0966).mp. (714)
- 3 (etodolac or lodine or ultradol).mp. (314)
- 4 (meloxicam or mobic).mp. (396)
- 5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (5905)
- 6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (422)
- 7 (cox-2 or cox2 or cox-II or coxII).mp. (5250)
- 8 cyclooxygenase inhibitors/ (8443)
- 9 or/1-8 (13332)
- 10 decision support techniques/ (4349)
- 11 markov.mp. (2519)
- 12 exp models economic/ (3561)
- 13 decision analysis.mp. (1854)
- 14 cost benefit analysis/ (31997)
- 15 or/10-14 (40654)
- 16 9 and 15 (43)

EMBASE (Ovid) 1980 to 2003 Week 47

- 1 (celecoxib or celebrex or sc-58635).mp. (2708)
- 2 (rofecoxib or vioxx or mk-0966).mp. (2118)
- 3 (etodolac or lodine or ultradol).mp. (1086)
- 4 (meloxicam or mobic).mp. (1066)
- 5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (5939)
- 6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (424)
- 7 (cox-2 or cox2 or cox-II or coxII).mp. (5342)
- 8 cyclooxygenase inhibitors/ (3412)
- 9 or/1-8 (13230)
- 10 exp arthritis/ (91818)
- 11 (arthrit\$ or osteoarthritis\$).mp. (72481)
- 12 or/10-11 (102255)
- 13 9 and 12 (2188)
- 14 decision support techniques/ (171)
- 15 markov.mp. (2076)
- 16 exp models economic/ (8061)
- 17 decision analysis.mp. (1691)

- 18 cost benefit analysis/ (16840)
- 19 or/14-18 (28072)
- 20 13 and 19 (23)

MEDLINE In-process and Other Non-indexed Citations (Ovid) 22 January 2004

- 1 (celecoxib or celebrex or sc-58635).mp. (120)
- 2 (rofecoxib or vioxx or mk-0966).mp. (79)
- 3 (etodolac or lodine or ultradol).mp. (6)
- 4 (meloxicam or mobic).mp. (24)
- 5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (320)
- 6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (33)
- 7 (cox-2 or cox2 or cox-II or coxII).mp. (527)
- 8 cyclooxygenase inhibitor\$.mp. (57)
- 9 or/1-8 (736)
- 10 decision support technique\$.mp. (0)
- 11 markov.mp. (249)
- 12 model\$.mp. (35510)
- 13 decision analysis.mp. (40)
- 14 cost benefit analysis.mp. (31)
- 15 or/10-14 (35620)
- 16 9 and 15 (117)

Costs/quality of life

MEDLINE (Ovid) 1966 to November Week 2 2003

- 1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (40)
- 2 (valdecoxib or bextra).mp. (81)
- 3 (lumiracoxib or prexige).mp. (6)
- 4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6313)
- 5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (440)
- 6 (cox-2 or cox2 or cox-II or coxII).mp. (5639)
- 7 cyclooxygenase inhibitors/ (8953)
- 8 (arthrit\$ or osteoarthrit\$).mp. (112138)
- 9 exp arthritis/ (120333)
- 10 or/1-7 (13329)
- 11 or/8-9 (135278)
- 12 10 and 11 (1165)
- 13 economics/ (26004)
- 14 exp "costs and cost analysis"/ (109788)
- 15 cost of illness/ (5730)
- 16 exp health care costs/ (21676)
- 17 economic value of life/ (7154)
- 18 exp economics medical/ (9939)
- 19 exp economics hospital/ (12664)

- 20 economics pharmaceutical/ (1296)
- 21 exp "fees and charges"/ (21639)
- 22 (econom\$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic\$).tw. (185564)
- 23 (expenditure\$ not energy).tw. (8121)
- 24 (value adj1 money).tw. (338)
- 25 budget\$.tw. (8462)
- 26 or/13-25 (291115)
- 27 12 and 26 (91)
- 28 from 27 keep 1-91 (91)

MEDLINE (Ovid) 1966 to January Week 2 2004

- 1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (40)
- 2 (valdecoxib or bextra).mp. (76)
- 3 (lumiracoxib or prexige).mp. (7)
- 4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (5905)
- 5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (422)
- 6 (cox-2 or cox2 or cox-II or coxII).mp. (5250)
- 7 cyclooxygenase inhibitors/ (8443)
- 8 or/1-7 (12738)
- 9 quality of life/ (38784)
- 10 life style/ (18785)
- 11 health status/ (22462)
- 12 health status indicators/ (7852)
- 13 value of life/ (4175)
- 14 quality of wellbeing.tw. (2)
- 15 or/9-14 (84063)
- 16 8 and 15 (30)

EMBASE (Ovid) 1980 to 2004 Week 4

- 1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (156)
- 2 (valdecoxib or bextra).mp. (284)
- 3 (lumiracoxib or prexige).mp. (48)
- 4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6202)
- 5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (439)
- 6 (cox-2 or cox2 or cox-II or coxII).mp. (5573)
- 7 cyclooxygenase inhibitors/ (3480)
- 8 (arthrit\$ or osteoarthrit\$).mp. (73407)
- 9 exp arthritis/ (93087)
- 10 or/1-7 (10986)
- 11 or/8-9 (103603)
- 12 10 and 11 (1387)
- 13 cost benefit analysis/ (17166)
- 14 cost effectiveness analysis/ (31987)
- 15 cost minimization analysis/ (607)

- 16 cost utility analysis/ (964)
- 17 economic evaluation/ (1725)
- 18 (cost or costs or costed or costly or costing).tw. (108193)
- 19 (economic\$ or pharmacoeconomic\$ or price\$ or pricing).tw. (50882)
- 20 (technology adj assessment\$).tw. (1029)
- 21 or/13-20 (161562)
- 22 10 and 21 (225)
- 23 11 and 22 (115)
- 24 exp quality of life/ (43795)
- 25 life style/ (14808)
- 26 health status/ (19424)
- 27 quality of wellbeing.mp. (5)
- 28 or/24-27 (73456)
- 29 12 and 28 (41)
- 30 23 or 29 (143)

MEDLINE In-process and Other Non-indexed Citations (Ovid) **22 January 2004**

- 1 (etoricoxib or arcoxia or mk-663 or mk-0663).mp. (10)
- 2 (valdecoxib or bextra).mp. (12)
- 3 (lumiracoxib or prexige).mp. (6)
- 4 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (320)
- 5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (33)
- 6 (cox-2 or cox2 or cox-II or coxII).mp. (527)
- 7 cyclooxygenase inhibitor\$.mp. (57)
- 8 or/1-7 (689)
- 9 (economic\$ or cost or costs or costly or costing or price or pricing or pharmacoeconomics).mp. (6456)
- 10 (expenditure\$ not energy).mp. [mp=title, abstract] (216)
- 11 (value adj1 money).mp. (15)
- 12 budget\$.mp. (293)
- 13 or/9-12 (6778)
- 14 8 and 13 (11)
- 15 quality of life.mp. (1953)
- 16 life style.mp. (103)
- 17 health status.mp. (408)
- 18 value of life.mp. (6)
- 19 quality of wellbeing.mp. (0)
- 20 or/15-19 (2405)
- 21 8 and 20 (7)
- 22 14 or 21 (17)

Cochrane Library Issue 4 2003

See search strategy for effectiveness above.

MEDLINE (Ovid) 1966 to November Week 2 2003

- 1 (celecoxib or celebrex or sc-58635).mp. (1003)

- 2 (rofecoxib or vioxx or mk-0966).mp. (751)
- 3 (etodolac or lodine or ultradol).mp. (312)
- 4 (meloxicam or mobic).mp. (408)
- 5 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (440)
- 6 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6313)
- 7 (cox-2 or cox2 or cox-II or coxII).mp. (5639)
- 8 cyclooxygenase inhibitors/ (8953)
- 9 exp arthritis/ (120333)
- 10 or/1-8 (13924)
- 11 9 and 10 (1115)
- 12 economics/ (26004)
- 13 exp "costs and cost analysis"/ (109788)
- 14 cost of illness/ (5730)
- 15 exp health care costs/ (21676)
- 16 economic value of life/ (7154)
- 17 exp economics medical/ (9939)
- 18 exp economics hospital/ (12664)
- 19 economics pharmaceutical/ (1296)
- 20 exp "fees and charges"/ (21639)
- 21 (econom\$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic\$).tw. (185564)
- 22 (expenditure\$ not energy).tw. (8121)
- 23 (value adj1 money).tw. (338)
- 24 budget\$.tw. (8462)
- 25 or/12-24 (291115)
- 26 11 and 25 (88)
- 27 from 26 keep 1-88 (88)

MEDLINE (Ovid) 1966 to January Week 2 2004

- 1 (celecoxib or celebrex or sc-58635).mp. (942)
- 2 (rofecoxib or vioxx or mk-0966).mp. (714)
- 3 (etodolac or lodine or ultradol).mp. (314)
- 4 (meloxicam or mobic).mp. (396)
- 5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (5905)
- 6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (422)
- 7 (cox-2 or cox2 or cox-II or coxII).mp. (5250)
- 8 cyclooxygenase inhibitors/ (8443)
- 9 or/1-8 (13332)
- 10 quality of life/ (38784)
- 11 life style/ (18785)
- 12 health status/ (22462)
- 13 health status indicators/ (7852)
- 14 value of life/ (4175)
- 15 quality of wellbeing.tw. (2)
- 16 or/10-15 (84063)
- 17 9 and 16 (35)

EMBASE (Ovid) 1980 to 2004 Week 4

- 1 (celecoxib or celebrex or sc-58635).mp. (2864)
- 2 (rofecoxib or vioxx or mk-0966).mp. (2253)
- 3 (etodolac or lodine or ultradol).mp. (1102)
- 4 (meloxicam or mobic).mp. (1099)
- 5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (6202)
- 6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (439)
- 7 (cox-2 or cox2 or cox-II or coxII).mp. (5573)
- 8 exp Cyclooxygenase 2 Inhibitor/ (8059)
- 9 exp Cyclooxygenase 2/ (5102)
- 10 or/1-9 (12921)
- 11 (arthrit\$ or osteoarthritis\$).mp. (73407)
- 12 exp arthritis/ (93087)
- 13 or/11-12 (103603)
- 14 cost benefit analysis/ (17166)
- 15 cost effectiveness analysis/ (31987)
- 16 cost minimization analysis/ (607)
- 17 cost utility analysis/ (964)
- 18 economic evaluation/ (1725)
- 19 (cost or costs or costed or costly or costing).tw. (108193)
- 20 (economic\$ or pharmacoeconomic\$ or price\$ or pricing).tw. (50882)
- 21 (technology adj assessment\$).tw. (1029)
- 22 or/14-21 (161562)
- 23 10 and 22 (445)
- 24 13 and 23 (204)
- 25 exp quality of life/ (43795)
- 26 life style/ (14808)
- 27 health status/ (19424)
- 28 quality of wellbeing.mp. (5)
- 29 or/25-28 (73456)
- 30 10 and 13 and 29 (104)
- 31 24 or 30 (281)

MEDLINE (Ovid) In-process and Other Non-indexed Citations 22 January 2004

- 1 (celecoxib or celebrex or sc-58635).mp. (120)
- 2 (rofecoxib or vioxx or mk-0966).mp. (79)
- 3 (etodolac or lodine or ultradol).mp. (6)
- 4 (meloxicam or mobic).mp. (24)
- 5 (cyclooxygenase-2 or cyclooxygenase2 or cyclooxygenase-II or cyclooxygenaseII).mp. (320)
- 6 (cyclo oxygenase-2 or cyclo oxygenase2 or cyclo oxygenase-II or cyclo oxygenaseII).mp. (33)
- 7 (cox-2 or cox2 or cox-II or coxII).mp. (527)
- 8 cyclooxygenase inhibitor\$.mp. (57)
- 9 or/1-8 (736)

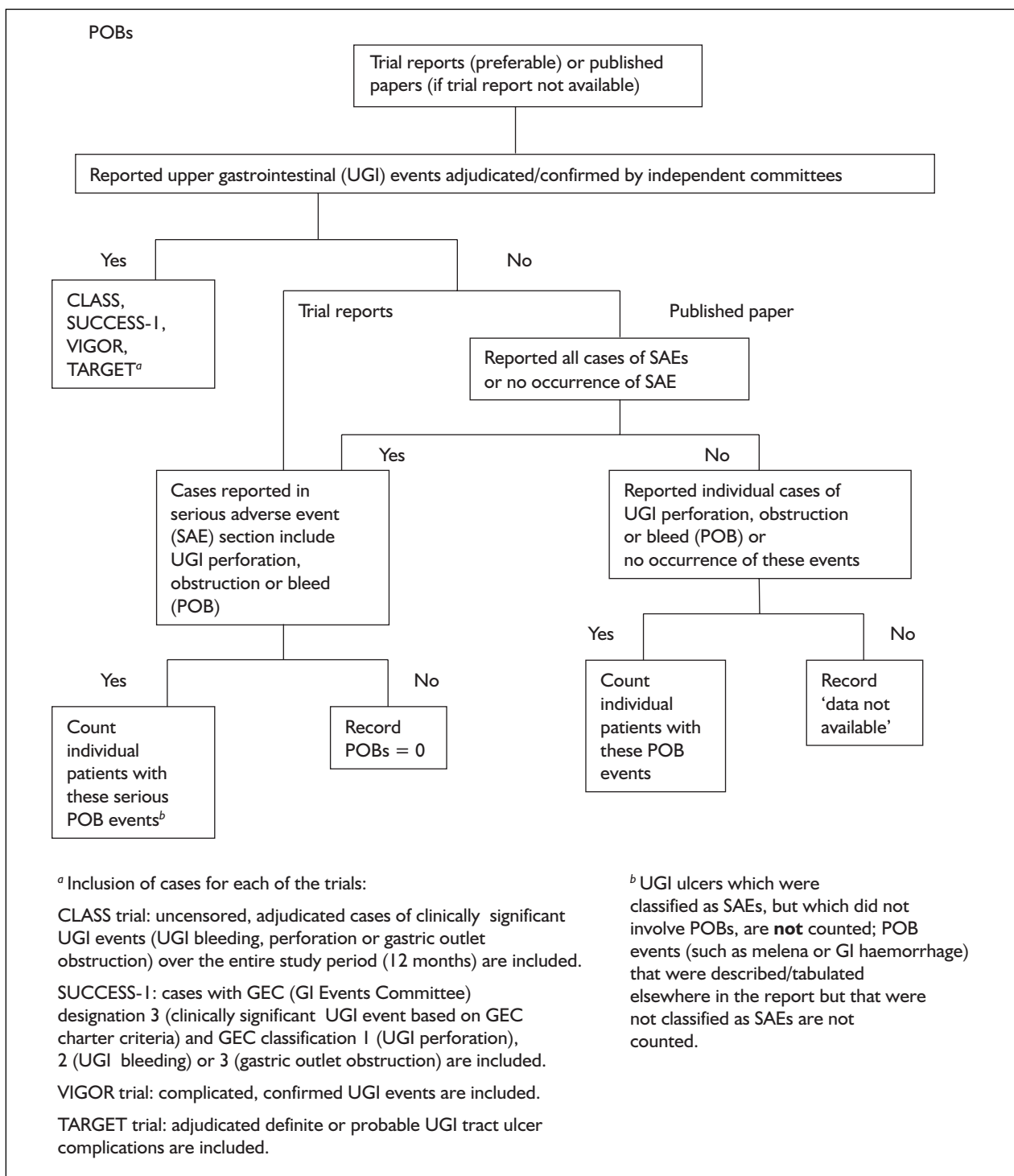
- 10 (econom\$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic\$).mp. (6615)
- 11 (expenditure\$ not energy).mp. (216)
- 12 (value adj1 money).mp. (15)
- 13 budget\$.mp. (293)
- 14 or/10-13 (6937)
- 15 9 and 14 (13)
- 16 quality of life.mp. (1953)
- 17 life style.mp. (103)
- 18 health status.mp. (408)
- 19 value of life.mp. (6)
- 20 quality of wellbeing.mp. (0)
- 21 or/16-20 (2405)
- 22 8 and 21 (0)
- 23 from 15 keep 1-13 (13)

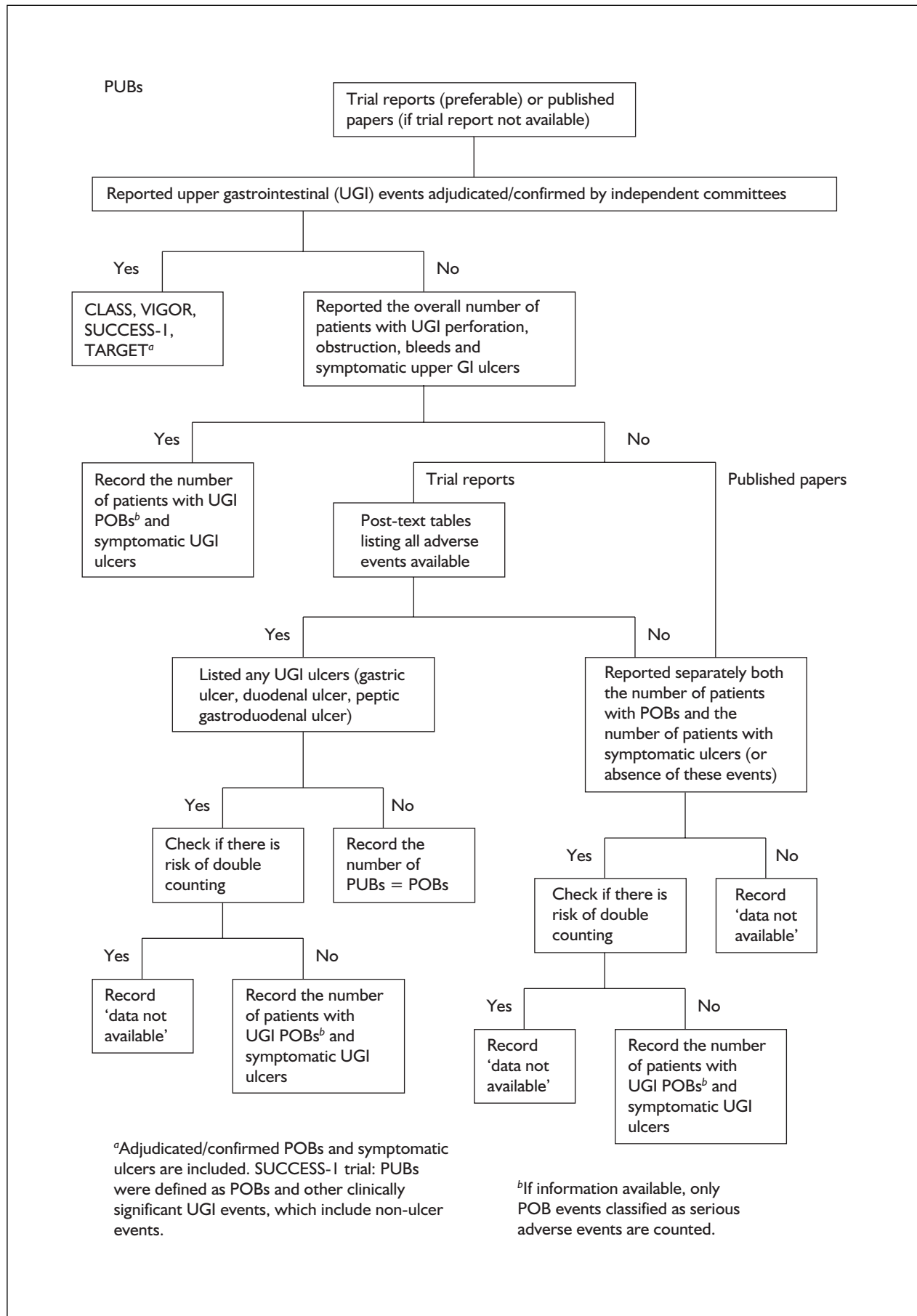
Quality of life of arthritis**MEDLINE(Ovid) 1966 to January Week 1 2004**

- 1 exp arthritis/ (118554)
- 2 quality of life/ (38688)
- 3 life style/ (18766)
- 4 health status/ (22407)
- 5 health status indicators/ (7839)
- 6 value of life/ (4175)
- 7 quality of wellbeing.tw. (2)
- 8 or/2-7 (83896)
- 9 (meta-analysis or review literature).sh. (5839)
- 10 metaanal\$.tw. (381)
- 11 meta-analy\$.tw. (10064)
- 12 (systematic\$ adj4 (review\$ or overview\$)).tw. (6090)
- 13 meta-analysis.pt. (8408)
- 14 review.pt. (990033)
- 15 case report.sh. (0)
- 16 letter.pt. (492568)
- 17 historical article.pt. (205338)
- 18 review of reported cases.pt. (48354)
- 19 review multicase.pt. (7866)
- 20 review.ti. (109665)
- 21 review literature.pt. (35109)
- 22 9 or 10 or 11 or 12 or 13 or 14 or 20 or 21 (1050467)
- 23 15 or 16 or 17 or 18 or 19 (748610)
- 24 22 not 23 (984099)
- 25 animals/ (3494785)
- 26 human.sh. (8239392)
- 27 25 not (25 and 26) (2705690)
- 28 24 not 27 (895681)
- 29 8 and 28 (11593)
- 30 1 and 29 (189)

Appendix 3

Algorithms for defining the number of patients with complicated UGI events (POBs) and clinical UGI events (PUBs)





Appendix 4

Rationale for data analysis approach to clinical effectiveness evidence

In order to generate a single estimate for each COX-2 selective NSAID for each decision analytic model, there was an opportunity to pool results within each COX-2 trial across a number of drug doses, across a range of follow-up durations, across trials of varying methodological quality, across a number of comparator non-selective NSAIDs and across OA and RA indications. In order to test the acceptability of this approach to pooling, an initial investigation was performed using one of the COX-2 selective NSAIDs (celecoxib) across a range of outcomes where various trials were available (i.e. VAS pain, withdrawal due to lack of efficacy, withdrawal due to GI-specific adverse events and level of MIs).

Heterogeneity was examined by univariate and multivariate meta-regression using study quality

(Jadad score), type of arthritis, choice of non-selective NSAID and follow-up as covariates. In addition, to assess the effect of COX-2 dose, results were stratified by drug dose.

As can be seen from the *Tables 110–113*, although there was some tendency for outcome to vary across COX-2 dose, there was no evidence of significant statistical heterogeneity in this or the other covariates across the various outcomes examined. In view of this, it was concluded that it was acceptable to pool trials within each COX-2 selective NSAID across COX-2 dose, across type of NSAID, across follow-up and across OA/RA. However, in addition to an overall pooled outcome result, results are also presented in the report stratified by COX-2 dose and for OA and RA separately.

TABLE 110 VAS pain – all NSAID versus all celecoxib doses

Mean difference (95% CI)		
Celecoxib 200 mg/day	-1.4 (-4.8 to 2.0)	
Celecoxib 400 mg/day	2.3 (-2.2 to 6.8)	
Celecoxib >400 mg/day	-0.8 (-2.0 to 0.4)	
Meta-regression	Univariate	Multivariate
Jadad	0.650	0.477
OA/RA	0.130	0.101
NSAID	0.533	0.907
Follow-up	0.40	0.229

TABLE 111 Withdrawal due to lack of efficacy – all NSAID versus all celecoxib doses

RR (95% CI)		
Celecoxib 200 mg/day	1.02 (0.86 to 1.21)	
Celecoxib 400 mg/day	1.02 (0.89 to 1.16)	
Celecoxib >400 mg/day	0.89 (0.74 to 1.07)	
Meta-regression	Univariate	Multivariate
Jadad	0.106	0.153
OA/RA	0.615	0.660
NSAID	0.267	0.198
Follow-up	0.644	0.499

TABLE 112 GI withdrawals – all NSAID versus all celecoxib doses

	RR (95% CI) [N trials]	
Celecoxib 200 mg/day	0.44 (0.35 to 0.56) [10]	
Celecoxib 400 mg/day	0.42 (0.30 to 0.57) [6]	
Celecoxib >400 mg/day	0.50 (0.39 to 0.65) [6]	
Meta-regression	Univariate	Multivariate
Jadad	0.260	0.823
OA/RA	0.177	0.173
NSAID	0.250	0.143
Follow-up	0.528	0.516

TABLE 113 MI – all NSAID versus all celecoxib doses

	RR (95% CI) [N trials]	
Celecoxib 200 mg/day	4.48 (0.83 to 24.1) [2]	
Celecoxib 400 mg/day	2.87 (1.02 to 8.06) [7]	
Celecoxib >400 mg/day	2.19 (0.38 to 12.5) [3]	
Meta-regression	Univariate	Multivariate
Jadad	0.922	0.939
OA/RA	0.827	0.830
NSAID	0.664	0.847
Follow-up	0.731	0.967

Appendix 5

Citations of excluded studies and list of trials excluded due to lack of information

Citations of excluded studies

Code	Reasons for exclusion	References excluded
A	Duration less than 2 weeks	336, 357, 369–372
B	Controlled trials without randomisation/observational studies with a control group	373–378
C	Observational studies without a control group	362, 379–386
D	Non-OA/RA patients	387, 388
E	Health volunteers	389–392
F	Trials with no relevant outcomes reported	393–400
G	Systematic reviews with no relevant outcomes reported	401–409
H	Interim trial reports	137, 348, 349, 352, 410
I	RCTs with no active/placebo comparators	363, 369, 411–414
J	Only abstract available	415, 416
K	Letters, editorials, comments, news without additional trial data	417–421
L	Not intervention of interest	422–426
M	Pooled analysis with no search strategy	32, 80–109, 427
N	Narrative review with no search strategy	428–434
O	Subtherapeutic doses and dose titrating studies	332–335, 337, 338, 340–347, 350, 351, 353, 354, 356
Z	Others	131, 132, 355, 435–437

List of trials which were excluded due to lack of information but otherwise met the inclusion criteria of the systematic review

Drug	Trial name/protocol number	COX-2 (dose per day)	Comparator (dose per day)	OA/RA	Duration of treatment	Sponsor	Information supplied by the sponsor	Comment
Meloxicam	Study 107.99 (Hertich, 1997 ³⁵⁸)	[Confidential information removed]	[Confidential information removed]			Boehringer Ingelheim	Trial synopsis	[Confidential information removed]
	Study 107.196 (Hsu, 1999 ³⁵⁹)	[Confidential information removed]	[Confidential information removed]			Boehringer Ingelheim	Trial synopsis	[Confidential information removed]
	Study 107.207	[Confidential information removed]	[Confidential information removed]			Boehringer Ingelheim	Trial synopsis	[Confidential information removed]
	Study 107.213	[Confidential information removed]	[Confidential information removed]			Boehringer Ingelheim	Trial synopsis	[Confidential information removed]
	Study 107.229	[Confidential information removed]	[Confidential information removed]			Boehringer Ingelheim	Trial synopsis	[Confidential information removed]
	Study 107.14 (Huskisson, 1994 ⁴¹⁶)	[Confidential information removed]	[Confidential information removed]			Boehringer Ingelheim	Trial summary	[Confidential information removed]
	Study 107.212	[Confidential information removed]	[Confidential information removed]			Boehringer Ingelheim	Trial synopsis	[Confidential information removed]
	Study 107.258	[Confidential information removed]	[Confidential information removed]			Boehringer Ingelheim	Trial synopsis	[Confidential information removed]
	Study 107.164	[Confidential information removed]	[Confidential information removed]			Boehringer Ingelheim	Trial synopsis	[Confidential information removed]
	Study 107.36 (Richardson, 1995 ⁴⁶⁰)	[Confidential information removed]	[Confidential information removed]			Boehringer Ingelheim	Trial summary	[Confidential information removed]
	Mazur, 1998 ⁴⁶¹	Meloxicam 7.5 mg (n = 40)	Diclofenac 100 mg (n = 30)	RA	3 weeks	Unknown	None (not company sponsored)	Moldova, double-blind RCT
Celecoxib	Pfizer Study 098 (M49-98-02-098)	[Confidential information removed]	[Confidential information removed]			Pfizer	None	'Trial report not finalised'
	Pfizer Study 100 (B49-98-02-100)	[Confidential information removed]	[Confidential information removed]			Pfizer	None	'Trial report not finalised'
	Pfizer Study A3191001	[Confidential information removed]	[Confidential information removed]			Pfizer	None	'Trial report not finalised'

continued

Drug	Trial name/protocol number	COX-2 (dose per day)	Comparator (dose per day)	OA/RA	Duration of treatment	Sponsor	Information supplied by the sponsor	Comment
	Pfizer Study A3191016	[Confidential information removed]	[Confidential information removed]			Pfizer	None	'Trial report not finalised'
	Pfizer Study A3191017					Pfizer	None	'Trial report not finalised'
	Pfizer Study A3191062	[Confidential information removed]	[Confidential information removed]			Pfizer	None	'Trial report not finalised'
	Pfizer Study A3191063	[Confidential information removed]	[Confidential information removed]			Pfizer	None	'Trial report not finalised'
	Pfizer Study A3191025	[Confidential information removed]	[Confidential information removed]			Pfizer	None	'Trial report not finalised'
	Pfizer Study A3191006/W49-99-02-124	[Confidential information removed]	[Confidential information removed]			Pfizer	None	'Trial report not finalised'
Rofecoxib	Study 090 (Geba, 2001 ³⁶⁴)	Rofecoxib 12.5 mg (n = 390)	Nabumetone 1000 mg (n = 392), placebo (n = 196)	OA	6 weeks	Merck Sharp and Dohme	Conference poster	Double-blind RCT
	Study C1 (Schnitzer, 2001 ⁴⁶⁴)	Rofecoxib 25 mg (n = 471)	Celecoxib 200 mg (n = 460), placebo (n = 151)	OA	6 weeks	Merck Sharp and Dohme	Conference poster	Double-blind RCT
	VACT-2 (Geba, 2003 ⁴⁶⁵)	Rofecoxib 12.5 mg (n = 259), 25 mg (n = 527)	Celecoxib 200 mg (n = 523), paracetamol (n = 269)	OA	6 weeks	Merck Sharp and Dohme	Conference poster	USA, double-blind RCT
	Study C2 (protocol 112)	[Confidential information removed]	[Confidential information removed]			Merck Sharp and Dohme	Trial synopsis	[Confidential information removed]
	Study 096 (Tritt, 2001b ³⁶⁷)	Rofecoxib 12.5 mg (n = 148), 25 mg (n = 311)	Naproxen 1000 mg (n = 149), placebo (n = 301)	RA	12 weeks	Merck Sharp and Dohme	Conference posters	Double-blind RCT
Etoricoxib	Study 018 (Fisher, 2001 ⁴⁶⁶)	Etoricoxib 60 mg (n = 222)	Naproxen 1000 mg (n = 218), placebo (n = 56)	OA	12 weeks	Merck Sharp and Dohme	Conference poster	Double-blind RCT

continued

Drug	Trial name/protocol number	COX-2 (dose per day)	Comparator (dose per day)	OA/RA	Duration of treatment	Sponsor	Information supplied by the sponsor	Comment
	Study 061, EDGE1	Etoricoxib 90 mg (n = 3593)	Diclofenac 150 mg (n = 3518)	OA	11–16.5 months	Merck Sharp and Dohme	Trial synopsis	Double-blind RCT
	Study 010 (Curtis, 2000 ⁴⁶⁷)	Etoricoxib 10 mg (n = 78), 60 mg (n = 126), 90 mg (n = 134), 120 mg (n = 120)	Placebo (n = 123)	RA	8 weeks	Merck Sharp and Dohme	Conference posters	Double-blind RCT

Appendix 6

Details of characteristics of included randomised controlled trials

Etodolac

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%)	Concurrent low-dose aspirin (%)	Disease condition and other comments
Bacon, 1990a, ^{136,137} Overview Efficacy of Etodolac 6 weeks	Etodolac 600 mg/day (300 mg b.d.) Naproxen 1000 mg/day (500 mg b.d.)	70 73	59.8 61.7	78 79	NR NR	All NSAIDs incl. aspirin withdrawn up to 14 days prior	Patients excl. if history of GI disease/GI haemorrhage within last 5 years	Excluded All NSAIDs incl. aspirin withdrawn up to 14 days prior	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Bacon, 1990b, ^{136,137} Overview Efficacy of Etodolac 12 weeks	Etodolac 600 mg/day (300 mg b.d.) Piroxicam 20 mg/day (20 mg o.d.)	170 165	59.5 58.1	77 75	NR NR	All NSAIDs incl. aspirin withdrawn up to 14 days prior	Patients excl. if history of GI disease/GI haemorrhage within last 5 years	Excluded All NSAIDs incl. aspirin withdrawn up to 14 days prior	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Bacon, 1990c, ^{136,137} Overview Efficacy of Etodolac 8 weeks	Etodolac 600 mg/day (200 mg t.d.s) Diclofenac 150 mg/day (50 mg t.d.s)	98 106	59.0 59.1	78 77	NR NR	All NSAIDs incl. aspirin withdrawn up to 14 days prior	Patients excl. if history of GI disease/GI haemorrhage within last 5 years	Excluded All NSAIDs incl. aspirin withdrawn up to 14 days prior	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Williams, 1989 ¹³⁸ UK 4 weeks	(Knee) Etodolac 600 mg/day (300 mg b.d.) Placebo (Hip) Etodolac 600 mg/day (300 mg b.d.) Placebo	50 54 54 52	62.9 62.7 61.3 64.0	64 59 48 50	5.1 5.2 4.7 4.2	N/A N/A N/A	– – –	– – –	OA (hip) Population: aged 18–75 years. Ongoing physical therapy allowed Exclusion: peptic ulcer disease or a history of GI bleeding within the past 5 years; anticoagulants, steroids, immunosuppressants and other NSAIDs not permitted

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%)	Concurrent low-dose (≤ 325 mg/day) aspirin (%)	Disease condition and other comments
Freitas, 1990 ¹³⁹ Brazil 8 weeks	Etodolac 600 mg/day (300 mg b.d.) Piroxicam 20 mg/day (20 mg o.d.)	33 32	53 50	97 81	NA 100?	100? 100?	- -	- -	OA (knee) Exclusion: patients with serious diseases were excluded, as were patients who were taking medication with a potential for interaction with NSAIDs. Baseline: duration of morning stiffness significantly longer in piroxicam group
Astorga Paulsen, 1991 ¹⁴³ Country NR, but likely to be Chile/Argentina/Portugal/Brazil 8 weeks	Etodolac 600 mg/day (300 mg b.d.) Piroxicam 20 mg/day (20 mg o.d.)	112 108	58 58	78 77	NR	Allowed but % not reported	CT CT	CT CT	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (no) Proportions of patients on this drug: Steroids: (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Brasseur, 1991 ¹⁴⁰ Belgium 6 weeks	Etodolac 600 mg/day (300 mg b.d.) Diclofenac SR 100 mg/day (100 mg o.d.)	32 29	63.3 60.2	81 69	NA NA	NA NA	- -	- -	OA (knee) Exclusion: patients who used anticoagulant, oral hypoglycaemic, hepatotoxic or corticosteroid drugs; patients who had taken investigational NSAIDs within 1 month of the study or etodolac at any time previously. Flare required. Diclofenac two-thirds of maximum recommended dose
Karbowski, 1991 ¹⁴¹ Country NR, probably Germany 6 weeks	Etodolac 600 mg/day (300 mg b.d.) Indomethacin 150 mg/day (50 mg t.d.s)	31 33	53.5 53.8	61 61	NR	Allowed % not given	CT CT	CT CT	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (no) Proportions of patients on this drug: Steroids: (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%)	Concurrent low-dose aspirin (%)	Disease condition and other comments
Palferman, 1991 ¹⁴² UK 6 weeks	Etodolac 600 mg/day (300 mg b.d.) Naproxen 1000 mg/day (500 mg b.d.)	29 27	61.6 64.5	59 67	NA NA	100 100	–	–	OA (knee) Inclusion: age 18–76 years. Exclusion: patients with a history of serious renal, hepatic or CV disease; chronic skin disease; GI bleeding or peptic ulcer disease; patients with clinically significant levels of rheumatoid factor. Patients who were receiving hypoglycaemic agents, anticoagulant therapy, any medication that caused liver enzyme abnormalities, corticosteroids within the previous 6 months, investigational NSAIDs within the previous month, or etodolac at any time previously were not eligible for the study. Paracetamol was allowed during the washout period and the first 7 days of the study. Flare was required for patients withdrawn from NSAIDs
Pena, 1991 ¹⁴⁴ Colombia 8 weeks	Etodolac 600 mg/day (300 mg b.d.) Naproxen 1000 mg/day (500 mg b.d.)	31 31	62.7 62.3	84 90	NA NA	100 100	–	–	OA (knee) Inclusion: age 18–75 years Exclusion: patients who had received oral corticosteroids in the previous 6 months or injection of corticosteroids within 4 weeks were not eligible. Paracetamol allowed during washout period

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%)	Concurrent low-dose aspirin (%)	Disease condition and other comments
Perpignano, 1991 ¹⁴⁵ Italy 4 weeks	Etodolac 600 mg/day (600 mg o.d.)	10	51.9	11/20 (55%)	Patients in acute phase requiring NSAIDs (acute phase defined by presence of at least 3 symptoms); no other details	No details (though states that patients underwent 7-day washout period)	Not stated, but patients excluded with peptic ulcer or who had an endoscopic score ≥ 2 (0–5 scale from normal mucosa = 0 to frank ulcer = 5)	No details	OA (knee, hip) Proportions if more than one site: knee (n = 10, 50%), hip (n = 10, 50%) Included patients taking GPA (can't tell) Included patients on anticoagulant (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
	Naproxen 750 mg/day (750 mg o.d.)	10	55.7						
Dick, 1992 ¹⁴⁶ Europe 6 weeks	Etodolac 600 mg/day (300 mg b.d.)	57	59.5	72	CT	Response required as inclusion criterion	No details	No details	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
	Piroxicam 20 mg/day (20 mg o.d.)	59	57.3	64					
Grisanti, 1992 ¹⁴⁷ Country NR 8 weeks	Etodolac 600 mg/day (200 mg t.d.s.)	85	59	86	NR	Allowed but % not reported	Peptic ulcer or GI bleed in the previous 5 years excluded	NR	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
	Diclofenac 150 mg/day (50 mg t.d.s.)	87	59	86					
Waterworth, 1992 ¹⁴⁸ Country not specified, but both authors from New Zealand 6 weeks	Etodolac 600 mg/day (300 mg b.d.)	28	59.8	43	NR	CT	CT	CT	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (no) NB: patients on steroids also excluded. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
	Piroxicam 20 mg/day (20 mg o.d.)	29	59.3	69					

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%)	Concurrent low-dose aspirin (≤325 mg/day) (%)	Disease condition and other comments
Burssens, 1993 ¹⁴⁹ Europe 4 weeks	Etodolac SR 600 mg/day (600 mg slow-release o.d.) Tenoxicam 20 mg/day (20 mg o.d.)	37 36	64 59	62 64	CT	Response required as inclusion criterion	Not stated, but patients with active peptic ulcer or a history of peptic ulcer or GI haemorrhage excluded	Not stated	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Eisenkolb, 1993 ¹⁵⁰ Europe 6 weeks	Etodolac 600 mg/day (200 mg t.d.s.) Diclofenac 150 mg/day (50 mg t.d.s.)	66 69	61.4 60.5	65 65	CT	Response required as inclusion criterion	–	–	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Chikanza, 1994 ¹⁵¹ 3 centres in UK 8 weeks (cross-over trial): 4 weeks for etodolac; and 4 weeks for naproxen)	Etodolac (E) 600 mg/day (300 mg b.d.) Naproxen (N) 1000 mg/day (500 mg b.d.) E–N N–E	39 37	61 63	9:30 8:29	NR	NR	NR	NR	OA (knee, hip) Included patients taking GPA (can't tell) Included patients on anticoagulant (can't tell) NB: patients on steroids within 6 months excluded Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Lucker, 1994 ¹⁵² Germany 3 months	Etodolac 600 mg/day (300 mg b.d.) Nimesulide 200 mg/day (100 mg b.d.)	99 100	63.7 65.0	66 68	NR	Use of NSAIDs a requirement for entry into trial	NR	NR	OA (knee) Included patients taking GPA (no) Included patients on anticoagulant (no) NB: steroid users also excluded Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%)	Concurrent low-dose aspirin (≤325 mg/day) (%)	Disease condition and other comments
Perpignano, 1994 ^{b3} Italy 8 weeks	Etodolac slow-release 600 mg/day (600 mg o.d.) Tenoxicam 20 mg/day (20 mg o.d.)	60 60	70.4 71.0	85 92	NR	% not given	Anyone with a <3 years history or GI ulcer/haemorrhage excluded	No	OA (knee, hip) Knee: etodolac = 49/60; tenoxicam = 44/60 Hip: etodolac = 11/60; tenoxicam = 16/60 Included patients taking GPA (can't tell) Included patients on anticoagulant (no) NB: no steroids allowed. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) NB: only those aged >65 years recruited
Dore, 1995 ¹⁵⁴ Country not stated, probably USA (11 centres) 4 weeks	Etodolac 800 mg/day (400 mg b.d.) Naproxen 1000 mg/day (500 mg b.d.) Placebo b.d.	86 82 86	63.8 63.7 63.6	60 63 65	NR	Allowed but % not given	Excluded	5 10 13	OA (knee) Included patients taking GPA (no) Included patients on anticoagulant (no) NB: recent steroid users excluded from trial Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Schnitzer, 1995 ¹⁵⁵ Country NR, probably USA 4 weeks	Etodolac 800 mg/day (400 mg b.d.) Nabumetone 1500 mg/day (1500 mg o.d.) Placebo	91 89 90	63.81 62.38 65.26	70.3 69.7 65.6	NR	Allowed % not reported	Major GI bleeding excluded	Allowed	OA (knee) Included patients taking GPA (no) Included patients on anticoagulant (no) Proportions of patients on this drug: Steroids: (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%)	Concurrent low-dose aspirin (%)	Disease condition and other comments
Jennings, 1997 ¹⁵⁶ USA 5 weeks	Etodolac 800 mg/day (400 mg b.d.) Naproxen 1000 mg/day (500 mg b.d.)	29 31	45.0 50.8	75.9 74.2	N/A	N/A	–	–	OA (foot, ankle) Etodolac higher than licensed (600 mg); naproxen group significantly older. Inconsistency in the number of patients included in analysis. Pain on motion, pain at night and impairment of productivity assessed but not reported. Reported results up to 3 weeks; 5-week results not reported Exclusion: history of stomach ulcer
Rogind, 1997 ¹⁵⁷ Denmark (19 centres) 8 weeks	Etodolac 600 mg/day (300 mg b.d.) Piroxicam 20 mg/day (20 mg o.d.)	138 133	67.0 67.5	79.7 77.4	NR NR	NR NR	Not stated, but patients with history of GI bleeding or gastric ulcer were excluded	Treatment with other kinds of anti-inflammatory drugs not allowed	OA (hip, knee) Proportions if more than one site: hip 41%, knee 59% Included population: OA of hip = 111; OA of knee = 160 Included patients taking GPA (no). Details of the GPA allowed and proportions: patients receiving H2-antagonists within previous 6 months were not eligible Included patients on anticoagulant (no). Proportions of patients on this drug: patients receiving anticoagulants within previous 6 months were not eligible Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Inclusion: patients with radiologically proven OA of hip or knee, showing at least 2 of the following: weight-bearing pain; joint stiffness; pain on motion. Age >40 years Exclusion: pregnant women; impaired renal or liver function; history of GI bleed or ulcer; inflammatory joint disease; allergy to aspirin or other NSAIDs; those on lithium, H2 antagonist, anticoagulant; steroids; penicillamine, gold, immunosuppressive or cytotoxic agents

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%)	Concurrent low-dose (≤ 325 mg/day) aspirin (%)	Disease condition and other comments
Schnitzer, 1997 ¹⁵⁸ USA 4 weeks NB: reports on three trials, only trial 1 extracted (2 and 3 reported elsewhere and already extracted)	Etodolac 800 mg/day (400 mg b.d.) Etodolac 800 mg/day (200 mg q.d.s.) Naproxen 1000 mg/day (500 mg b.d.) Placebo	106 105 109 104	62.6 65.2 62.2 63.8	80 72 70 80	Not stated	Some patients previously on long-acting NSAIDs, but number not stated	Patients with history of GI bleeding or ulcers excluded	≥ 325 mg/day aspirin permitted; number of patients not stated	OA (knee) GPA allowed in during the trial (can't tell) Included patients on steroids (no) and/or anticoagulants (can't tell). Proportions of patients on these drugs: use of corticosteroids not permitted Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Taha, ^{159,160} UK, single centre, 4 weeks	Etodolac 600 mg/day (300 mg b.d.) Naproxen 1000 mg/day (500 mg b.d.)	15 ^e 15 ^e	50 57	73.3 66.7	11 6	80 80	NR NR	NR NR	RA Included patients taking GPA (no) Included patients on steroids (no) and/or anticoagulants (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Included functional class I, II, III
Delcambre, 1990 ³³⁹ France 14 centres 6 weeks	Etodolac 600 mg/day (200 mg t.d.s.) Indomethacin (100 mg/day (25 mg b.d. and 50 mg o.d.))	50 52	56.5 56.8	17.3 (based on 98 patients: 17 female, 81 male, 4 missing values)	9.0 7.5	NR	No details	No details	RA Included patients taking GPA (can't tell) Included patients on steroids (yes): 37 patients (36.2%), 17 in etodolac arm, 20 in indomethacin arm and/or anticoagulants (can't tell). Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Included functional class I, II, III (one of the inclusion criteria was being in functional class I, II or III)

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%)	Concurrent low-dose aspirin (%)	Disease condition and other comments
Taha, 1990 ^{160,162} UK, single centre 4 weeks	Etodolac 600 mg/day (300 mg b.d.) Naproxen 1000 mg/day (500 mg b.d.)	14 ^f 13 ^f	50 60	71.4 69.2	NR NR	78.6 76.9	0 0 (excluded)	Can't tell	RA Included patients taking GPA (no) Included patients on steroids (no) and/or anticoagulants (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Included functional class I, II, III, (according to Russell, 1990 ¹⁶⁰)
Lightfoot, 1997 ¹⁶³ USA and Europe 12 weeks	Etodolac 400 mg/day (200 mg b.d.) Etodolac 600 mg/day (300 mg b.d.) Piroxicam 20 mg/day (20 mg o.d.)	140 ^g 147 ^g 139 ^g	57 58 56	75 60 69	>6 months	Response required as inclusion criterion	NR	NR	RA Included patients taking GPA (can't tell) Included patients on steroids (yes) and/or anticoagulants (can't tell) Proportions of patients on these drugs: Etodolac 200 51 (36%) Etodolac 300 55 (37%) Piroxicam 20 50 (36%) DMARD or steroid dose to be unchanged during study Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Included functional class (can't tell)

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%)	Concurrent low-dose aspirin (%)	Disease condition and other comments
Neustadt, 1997 ⁶⁴ USA 3 years	Etodolac 300 mg/day (150 mg b.d.) Etodolac 1000 mg/day (500 mg b.d.) Ibuprofen 2400 mg/day (600 mg q.d.s.)	620 409 417	53.2 53.0 53.1	71 69 72	3.6 3.5 3.6	Response required as inclusion criterion	Can't tell	Can't tell	RA Included patients taking GPA (can't tell) Included patients on steroids (yes) and/or anticoagulants (can't tell) Proportions of patients on these drugs: treatment with low-dosage oral corticosteroids (≤ 5 mg/day prednisolone or equivalent) was permitted during the study provided the dose remained constant over the 4 weeks before the patient enrolled in the study. About 20% of patients used low dosage corticosteroids. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Included functional class I, II

CT, can't tell; GPA, gastroprotective agent; NA, not applicable; NR, not reported; SD, standard deviation.

^a Duration of follow-up.

^b Dose per day.

^c Number of randomised.

^d Values are means unless specified otherwise.

^e Thirty-two patients were randomised but two were excluded: one patient failed to attend the final visit and one took medications prohibited by the protocol.

^f Twenty-nine patients were randomised but two patients who dropped out before completing the study due to protocol violations were excluded.

^g Of the 426 patients enrolled, 65 were excluded from efficacy analysis for protocol violations.

Meloxicam

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Carrabba, 1995 ^{168,169} Italy, Germany (24 centres) 3 weeks	Meloxicam 15 mg/day (15 mg o.d.) Piroxicam 20 mg/day (20 mg o.d.)	216 109 ^f	61 62	85 84	5.8 5.9	Not stated	–	–	OA (hip, knee) Corticosteroids allowed at stabilised dose Paracetamol \leq 4 g/day allowed
Hosie, 1996 ¹⁷⁰ UK 6-months	Meloxicam 7.5 mg/day (7.5 mg o.d.) Diclofenac SR 100 mg/day (100 mg o.d.)	169 167 ^g	64 64	59 59	5.6 7.0	NR	–	–	OA (hip, knee) Excluded patients if: evidence of active peptic ulceration Paracetamol rescue therapy (\leq 4 g/day) allowed but no other NSAIDs
Linden, 1996 ¹⁶⁵ (Sweden, Denmark, Belgium, The Netherlands) (22 centres) 6 weeks	Meloxicam 15 mg/day (15 mg o.d.) Meloxicam 30 mg/day (30 mg o.d.) Piroxicam 20 mg/day (20 mg o.d.)	129 ? 127	67 ? 67	63 ? 63	6.2 ? 5.5	Not stated	–	–	OA (hip) Treatment with other NSAIDs and analgesics not allowed Paracetamol as rescue therapy allowed
Goei The, 1997 ¹⁶⁶ Belgium, Germany, The Netherlands (23 centres) 6 weeks	Meloxicam 15 mg/day (15 mg o.d.) Meloxicam 30 mg/day (30 mg o.d.) Diclofenac SR 100 mg/day (100 mg o.d.)	128 ? 130	72 ? 71	85 ? 82	7.6 ? 7.3	Not stated	–	–	OA (knee) Other NSAIDs and intra-articular steroids not allowed Paracetamol rescue therapy allowed (\leq 4 g/day)

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (≤ 325 mg/day) aspirin (%)	Disease condition and other comments
Hosie, 1997 ¹⁷¹ UK 6-months	Meloxicam 15 mg/day (15 mg o.d.) Piroxicam 20 mg/day (20 mg o.d.)	306 149	66 ^h 64 ^h	58 54	5 5	Not stated	–	–	OA (hip and knee) Excluded patients treated within last 3 months with anti-ulcer drugs or evidence of ulcer within last 6 months Paracetamol ≤ 4 g/day as 'rescue therapy' allowed
Dequeker, 1998 ¹⁷² SELECT Trial International 28 days	Meloxicam 7.5 mg/day (7.5 mg o.d.) Piroxicam 20 mg/day (20 mg o.d.)	4320 4336	61.3 61.6	68 67	3.8 4.0	79 79	6.4 5.6	Proportions not available	OA (knee, spine, hip, hand) Proportions if more than one site: Meloxicam: knee 46%; spine 28%; hip 14%; hand 12%. Piroxicam: knee 44%; spine 30%; hip 15%; hand 11%. Included patients taking GPA (yes). Includes antacids, PPI and H2-blockers. Meloxicam 4.6%; piroxicam 5.6%. Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell). Not described, presumably not assessed
Hawkey, 1998 ¹⁷³ MELISSA Trial International 28 days	Meloxicam 7.5 mg/day (7.5 mg o.d.) Diclofenac SR 100 mg/day (100 mg o.d.)	4635 4688	61.5 61.7	66.8 67.2	4.3 4.0	81.9 82.1	4.8 5.3	Proportions not available	OA (knee, spine, hip, hand) Proportions if more than one site: Meloxicam: knee 45%; spine 28%; hip 15%; hand 12%. Diclofenac: knee 41%; spine 30%; hip 17%; hand 12%. Included patients taking GPA (yes). Includes antacids, PPI and H2-blockers. Meloxicam 5.6%; piroxicam 6.4%. Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell). Not described, presumably not assessed

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Lund, 1998 ^{174,175} Sweden,	Meloxicam 7.5 mg/day (7.5 mg o.d.)	140	70	64	8.7	NR	–	–	OA (knee) Results for the 30 mg meloxicam group not reported
Denmark, Belgium, The Netherlands, Germany (multicentre) 3 weeks	Meloxicam 15 mg/day (15 mg o.d.) Meloxicam 30 mg/day (30 mg o.d.) Placebo	134 102 137	68 – 68	75 – 75	8.5 – 8.0				Rescue paracetamol allowed and treatment with other NSAIDs not allowed
Yocum, 2000 ^{176–178} USA 12 weeks	Meloxicam 3.75 mg/day (3.75 mg o.d.) Meloxicam 7.5 mg/day (7.5 mg o.d.) Meloxicam 15 mg/day (15 mg o.d.)	154 154 156	62 62 64	67 63 64	9 8 7	100 100 100	– – –	– – –	OA (hip, knee) Excluded patients with UGI perforations, ulcers or peptic ulcer bleeding \leq 6 months, or long-term use of GI medications that could not be stopped during period of study
	Diclofenac 100 mg/day (50 mg b.d.) Placebo	153 157	63 62	68 65	9 8	100 100			
Chang, 2001 ¹⁷⁹ Taiwan 4 weeks	Meloxicam 7.5 mg/day (7.5 mg o.d.) Piroxicam 20 mg/day (20 mg o.d.)	36 36	61 63	89 75	2.8 5.9	100 100	– –	Not allowed	OA (knee) Excluded if previous endoscopically detected ulcer No concurrent medications allowed (including low-dose aspirin, other NSAIDs, > 4 g/day paracetamol) Concomitant < 4 g/day paracetamol and antacid drugs allowed

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (≤325 mg/day) (%)	Disease condition and other comments
Valat, 2001 ¹⁸⁰ Belgium, Italy, France (10 centres) 2 weeks	Meloxicam 7.5 mg/day (7.5 mg o.d.) Diclofenac SR 100 mg/day (100 mg o.d.)	117 112	58 57	86 88	9.2 10.1	NR NR	NR NR	NR NR	OA (lumbar spine) Included patients taking GPA (can't tell) Included patients on steroids (no) Included patients <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed
Xu, 2002 ¹⁸¹ China multicentre 4 weeks	Meloxicam 7.5 mg/day (7.5 mg o.d.) Nabumetone 1000 mg/day (1000 mg o.d.)	31 29	54 55	90 83	NR NR	NR NR	NR NR	NR NR	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (can't tell). Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Population: age ≥40 years. Exclusion: patients with (current?) GI bleeding or gastric/duodenal ulcer Possibly 63 patients randomised (meloxicam 32, nabumetone 31). Three excluded from the study: lost to follow-up (meloxicam 1, nabumetone 1); withdrawal due to lack of efficacy, duration of treatment less than half of the study period (nabumetone 1)

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Wojtuleswski, 1996 ^{182,183} Europe and Mexico (48 centres) 6 months	Meloxicam 7.5 mg/day (7.5 mg o.d.) Naproxen 750 mg/day (250 mg t.d.s)	199	18–75	Not stated	9.3	86	–	–	RA Patients with history of previous gastric ulcer excluded I.m. or i.v. glucocorticosteroids or adrenocorticotrophic hormones ≤ 2 intrarticular injections/month and paracetamol ≤ 4 g/day allowed
Lemmel, 1997 ^{184,185} Europe and Mexico (59 centres) 3 weeks	Meloxicam 7.5 mg/day (7.5 mg o.d.) Meloxicam 15 mg/day (15 mg o.d.) Placebo	159 162 147	55 54 55	Not stated	10.1 10.0 10.2	Not stated	–	–	RA History of active ulcer within last 6 months excluded Gold, penicillamine, methotrexate, azathioprine, sulfasalazine, antimalarials, prednisolone (≤ 7.5 mg/day if taken before trial) and paracetamol (≤ 4 g/day) allowed. Included functional class (I, II, III)
Furst, 2002 ^{167,186} USA 12 weeks	Meloxicam 7.5 mg/day (7.5 mg o.d.) Meloxicam 15 mg/day (15 mg o.d.) Meloxicam 22.5 mg/day (22.5 mg o.d.) Diclofenac 150 mg/day (75 mg b.d.) Placebo	175 184 177 181 177	56 56 57 55 56	79 76 73 78 75	10 10 10 10 10	100 100 100 100 100	12.0 8.7 10.7 9.9 9.0	–	RA DMARDs allowed if taking ≥ 3 months prior to trial Acetaminophen allowed but not ≤ 12 hours assessment points Steroids (not allowed but given in some cases)

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (≤ 325 mg/day) aspirin (%)	Disease condition and other comments
Xu, 2002b ^{187,188} China 4 weeks	Meloxicam 15 mg/day (15 mg o.d.) Nabumetone 1000 mg/day (1000 mg o.d.)	59 61	46 47	79.7 86.9	5.8 5.2	NR NR	NR NR	NR NR	RA Included patients taking GPA (can't tell) Included patients on steroids (no) and/or anticoagulants (can't tell). Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Included functional class (I, III) No mention of concurrent medications. 128 patients initially randomised; 8 excluded (4 from each arm) from all analyses

^a Duration of follow-up.
^b Dose per day.
^c Number of randomised.
^d Values are means unless specified otherwise.
^e Prior GI ulcers.
^f 2 to 1 randomisation.
^g Data on one patient 'omitted from database in error'.
^h Median.

Celecoxib

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (≤325 mg/day) aspirin (%)	Disease condition and other comments
Simon, 1998 ¹⁹⁰ USA 2 weeks Pfizer Study 013	Celecoxib 80 mg/day (40 mg b.d.) 200 mg/day (100 mg b.d.) 400 mg/day (200 mg b.d.) Placebo	71 73 76 73	61 61 63 62	65 65 75 73	9.3 9.8 9.0 11.7	NR NR NR NR	NR ^f NR ^f NR ^f NR ^f	NR ^g NR ^g NR ^g NR ^g	OA (knee) Included patients taking GPA (can't tell) Included patients on steroids (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (I, II, III)
Bensen, 1999 ¹⁹¹⁻¹⁹³ USA 97 centres 12 weeks Pfizer Study 020	Celecoxib 100 mg/day (50 mg b.d.) Celecoxib 200 mg/day (100 mg b.d.) Celecoxib 400 mg/day (200 mg b.d.) Naproxen 1000 mg/day (500 mg b.d.) Placebo	218 217 222 216 220	62 63 62 62 62	73 72 71 75 69	10 9 10 11 9	NR NR NR NR NR	NR ^f NR ^f NR ^f NR ^f NR ^f	NR NR NR NR NR	Included patients taking GPA (can't tell) Included patients on steroids (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (I, II, III)
Williams, 2000 ¹⁹⁴ USA 50 centres 6 weeks Pfizer Study 060	Celecoxib 200 mg/day (100 mg b.d.) 200 mg/day (200 mg o.d.) Placebo	231 223 232	63.0 62.7 62.6	66 67 67	8.6 9.3 8.8	NR NR NR	NR ^f NR ^f NR ^f	11-23% 11-23% 11-23%	OA (knee) Included patients taking GPA (can't tell) Included patients on steroids (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (I, II, III)

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (\leq 325 mg/day) aspirin (%)	Disease condition and other comments
[Confidential information removed]									
Goldstein, 2001 ^b , ^{195,224} USA	Celecoxib 200 mg/day (100 mg b.d.)	4421							
1142 centres, 37 countries 12 weeks	Celecoxib 400 mg/day (200 mg b.d.)	4429							
SUCCESS-I Pfizer Study 096 (Pfizer 2004 submission)	Diclofenac ^h 100 mg/day (50 mg b.d.)	3510							
	Naproxen ^h 1000 mg/day (500 mg b.d.)	914							
Kivitz, 2001 ¹⁹⁶ USA and Canada	Celecoxib 100 mg/day (50 mg b.d.)	216	62	65	7.3	NR	NR	NR	OA (hip) Included patients taking GPA (can't tell) Included patients on steroids (yes)
176 centres 12 weeks Pfizer Study 054	Celecoxib 200 mg/day (100 mg b.d.)	207	62	65	7.2	NR	NR	NR	Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
	Celecoxib 400 mg/day (200 mg b.d.)	213	61	67	6.9	NR	NR	NR	HP therapy not allowed Included functional class (I, II, III)
	Naproxen 1000 mg/day (500 mg b.d.)	207	64	66	7.3	NR	NR	NR	
	Placebo	218	64	67	7.9	NR	NR	NR	

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
McKenna, 2001 ^b , ¹⁹⁷ USA 20 centres 6 weeks Pfizer Study 152	Celecoxib 200 mg o.d. Rofecoxib 25 mg o.d. Placebo	63 59 60	62 61.5 63	67 71 75	11.2 10.1 11.5	71 81 83	10 5 12	NR NR NR	OA (knee) Included patients taking GPA (no) Included patients on steroids (can't tell) Included patients on anticoagulants (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (I, II, III)
McKenna, 2001 ^a , ¹⁹⁸ UK 6 weeks Pfizer Study 118	Celecoxib 200 mg/day (100 mg b.d.) Diclofenac 150 mg/day (50 mg t.d.s.) Placebo	199 200 201	62 63 60	68 62 66	8.4 8.5 8.8	77.6 78.4 77.5	4 3 4.5	NR NR NR	OA (knee) Included patients taking GPA (can't tell) Included patients on steroids (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (can't tell)
Pfizer Study 021 (Pfizer 2000 submission)	[Confidential information removed]								
McKenna, 2002 ¹⁹⁹ Multicentre 6 weeks Pfizer Study 042	Celecoxib 200 mg/day (100 mg b.d.) Diclofenac 100 mg/day (50 mg b.d.)	346 341	63.3 64.1	71 72	7.3 6.6	NR NR	2.6 2.6	7.8 8.8	OA (hip, knee) Included patients taking GPA (can't tell) Included patients on steroids (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (can't tell)
Pfizer Study 047 (Pfizer 2000 submission)	[Confidential information removed]								

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (\leq 325 mg/day) aspirin (%)	Disease condition and other comments
Whelton, 2002 ^{282,283} SUCCESS VI USA and Canada (101 centres) 6 weeks Pfizer Study 149	Celecoxib 200 mg/day (200 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.)	411 399	74.0 74.1	66.5 66.4	13.6 11.7	NR NR	NR NR	37.9 37.1	OA (hip, hand, knee) Included patients taking GPA (can't tell) Included patients on steroids (no) Details or anticoagulants (yes) Proportions not reported Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (I, II, III)
Williams, 2001 ²⁰⁰ USA 6 weeks Pfizer Study 087	Celecoxib 200 mg/day (100 mg b.d.) Celecoxib 200 mg/day (200 mg o.d.) Placebo	243 231 244	62 61 61	69 69 73	9.5 9.4 9.7	NR NR NR	NR NR NR	NR NR NR	OA (knee) Included patients taking GPA (can't tell) Included patients on steroids (no) Proportions of patients on these drugs: NR Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (I, II, III)
Suarez-Otero, 2002 ²⁰¹ Mexico 6 weeks	Celecoxib 200 mg/day (100 mg b.d.) Diclofenac- cholestyramine 280 mg/day (140 mg b.d.)	40 41	56 59	NR NR	3.2 3.4	NR NR	NR NR	NR NR	OA (knee, hand, hip) Included patients taking GPA (no) Included patients on steroids (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (I, II, III)

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (\leq 325 mg/day) aspirin (%)	Disease condition and other comments
Whelton, 2002a ²⁸⁴ SUCCESS VII USA and Canada. 6 weeks Pfizer Study 181	Celecoxib 200 mg/day (200 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.)	549 543	73.3 73.1	63.9 60.1	11.7 10.1	NR NR	NR NR	NR NR	OA (hip, knee, hand) Patients with OA of hip, knee or hand included but proportions not reported. Included patients taking GPA (can't tell) Included patients on anticoagulant (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell). No indication that this was tested. This study compares half of the maximum permitted dose of celecoxib (400 mg) for OA versus the full permitted dose of rofecoxib (25 mg)
Gibofsky, 2003 ²⁰² USA and Canada 6 weeks Pfizer Study 003	Celecoxib 200 mg/day (200 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.) Placebo	189 190 96	62.2 63.4 63.1	69 66 65	8.6 8.8 8.3	NR NR NR	6 5 6	NR NR NR	OA (knee) Included patients taking GPA (can't tell) Included patients on steroids (no) Included patients on anticoagulants (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Included functional class (I, II, III)
Hawel, 2003 ²⁰³ Austria 2 weeks (15 days)	Dexibuprofen 800 mg/day (400 mg b.d.) Celecoxib 200 mg/day (100 mg b.d.)	74 74	NR NR	55 43	NR NR	NR NR	NR NR	NR NR	OA (hip) Included patients taking GPA (can't tell) Included patients on steroids (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (can't tell)

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (\leq 325 mg/day) aspirin (%)	Disease condition and other comments
Pincus, 2004 ^a , 204, USA	Celecoxib 200 mg/day (200 mg o.d.) ^f	181	64.5	61	9.5	NR	NR	NR	OA (hip, knee) Included patients taking GPA (can't tell) Included patients on steroids (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (can't tell)
6 weeks \times 2 PACEsa Pfizer Study 010	Acetaminophen 4 g per day (1000 mg q.d.s.) ^f	171	63.6	62	9.7	NR	NR	NR	
	Placebo ^f	172	62.6	64	9.3	NR	NR	NR	
Sowers, 2003 ^a , 206, 249 CRESCENT, Pfizer Study 002	Celecoxib 200 mg/day (200 mg o.d.)	136	[Confidential information removed]						
12 weeks (Pfizer 2004 submission)	Rofecoxib 25 mg/day (25 mg o.d.)	138							
	Naproxen 1000 mg/day (500 mg b.d.)	130							
Pincus, 2004 ^b , 204 USA	Celecoxib 200 mg/day (200 mg o.d.) ^f	189	63.5	67	9.3	NR	NR	NR	OA (hip, knee) Included patients taking GPA (can't tell) Included patients on steroids (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (can't tell)
6 weeks \times 2 PACEsb Pfizer Study 249	Acetaminophen 1000 mg q.d.s. ^f	185	63.6	63	9.9	NR	NR	NR	
	Placebo ^f	182	62.6	64	8.7	NR	NR	NR	
Simon, 1998 ^b , 190 USA	Celecoxib 80 mg/day (40 mg b.d.)	81	55.6	67	9.7	NR	NR ^g	NR ^g	RA Included patients taking GPA (can't tell) Included patients on steroids (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (I, II, III)
4 weeks Pfizer Study 012	400 mg/day (200 mg b.d.)	82	55.5	89	10.9	NR	NR ^g	NR ^g	
	800 mg/day (400 mg b.d.)	82	56.7	79	10.5	NR	NR ^g	NR ^g	
	Placebo	85	56.5	75	12.8	NR	NR ^g	NR ^g	

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Emery, 1999 ²¹ Multicentre, worldwide 132 centres 24 weeks Pfizer Study 041	Celecoxib 400 mg/day (200 mg b.d.) Diclofenac 150 mg/day (75 mg b.d.)	326 329	56 55	76 71	[Confidential information removed]	NR NR	9 8	0 0	RA Included patients taking GPA (no Details of GPA allowed and proportions: GPA not allowed Included patients on steroids (yes) Included patients on anticoagulants (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (yes) Numbers not reported Included functional class (I, II, III)
Simon, 1999 ^{21,2,13} USA and Canada (79 centres) 3 months Pfizer Study 022	Celecoxib 200 mg/day (100 mg b.d.) 400 mg/day (200 mg b.d.) 800 mg/day (400 mg b.d.) Naproxen 1000 mg/day (500 mg b.d.) Placebo	240 235 218 225 231	54 55 54 55 54	74 73 78 79 77	11 11 10 10 11	NR NR NR NR NR	10 11 6 8 8	RA Included patients taking GPA (no) Details of GPA allowed and proportions: Antiulcer drugs prohibited Included patients on steroids (yes) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (I, II, III)	
Pfizer Study 023, 1998 ²⁷ (Pfizer 2000 submission)	[Confidential information removed]								

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (≤325 mg/day) (%)	Disease condition and other comments
Silverstein, 2000 ^{50,54,215-219} CLASS study, USA and Canada, multicentre >26 weeks	Celecoxib 800 mg/day (400 mg b.d.) Diclofenac 150 mg/day (75 mg b.d.)	3987 (27.2% RA)	60.6	68.6	OA >10, RA >11	81.4	8.4	20.9	RA and OA (location not stated) Included patients taking GPA (no) Details of the GPA allowed and proportions: Short-term use of antacids (up to 7 days per month) and calcium containing antacids as supplements allowed. Included patients on steroids (yes) and/or anticoagulants (yes)
Pfizer Study 035/102	Ibuprofen 2400 mg/day (800 mg t.d.s.)	1985 (27.6% RA)	59.5	70.8	OA 9.9 RA 10.9	81.6 ^f	8.5	19.3	Proportions of patients on these drugs: Steroids: celecoxib 30.6%, diclofenac 28.5%, ibuprofen 30.6%. Anticoagulants: celecoxib 1.1%, diclofenac 1.2%, ibuprofen 1.0%. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (yes). HP therapy not permitted. Positive patients: celecoxib 38.6%, diclofenac 37.7%, ibuprofen 38.7%. Included functional class (can't tell). No restrictions apparent. Patients with a positive faecal occult blood screening test were excluded
Goldstein, 2001 ^{20,269} USA 75 centres 3 months Pfizer Study 062	Celecoxib 400 mg/day (200 mg b.d.) Naproxen 1000 mg/day (500 mg b.d.)	270 267	57 58	67 67	9.5/11.6 11.0/8.9	Not stated	7.8 7.5	Not stated ^f	RA and OA (73%) Included patients taking GPA (no) Details of GPA allowed and proportions: GPA not allowed Included patients on steroids (yes) 5.2/3.4% Included patients anticoagulants (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy: HP therapy not permitted. Positive patients: 12.2/12.3% Included functional class (I, II, III)

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Pfizer Study 071 ²²⁶ (Pfizer 2000 submission)	[Confidential information removed]								
Chan, 2002 ⁵⁹ Hong Kong 6 months	Celecoxib 400 mg/day (200 mg b.d.) + placebo Diclofenac 150 mg/day (75 mg b.d.) + omeprazole 20 mg/day (20 mg o.d.)	144 143	67 69	39 35	NR NR	NR NR	100 100	6.2 12.6	RA and OA (location not stated) Included patients taking GPA (no) Included patients on steroids (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (no) HP+ patients excluded Included functional class (can't tell) OA 87%, RA 2% and Other 11%
Pfizer Study 105 ⁴⁴⁵ (Pfizer 2004 submission)	[Confidential information removed]								
Pfizer Study 106 ⁴⁴⁶ (Pfizer 2004 submission)	[Confidential information removed]								
Pfizer Study 107 ⁴⁴⁷ (Pfizer 2004 submission)	[Confidential information removed]								
Pfizer Study 209 ⁴³⁹ (Pfizer 2004 submission)	[Confidential information removed]								

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (≤ 325 mg/day) aspirin (%)	Disease condition and other comments
Pfizer Study 211 ²²⁵ (Pfizer 2004 submission)	[Confidential information removed]								
Pfizer Study 210 ⁴⁴⁰ (Pfizer 2004 submission)	[Confidential information removed]								
Pfizer Study 216 ²²³ (Pfizer 2004 submission)	[Confidential information removed]								

^a Duration of follow-up.
^b Dose per day.
^c Number of randomised.
^d Values are means unless specified otherwise.
^e Prior GI ulcers unless specified otherwise.
^f Patients with active GI disease were excluded.
^g Low-dose aspirin (≤ 325 mg/day) was allowed but the proportion of patients who received it was not reported.
^h Naproxen was administered to patients in the United States and Canada; diclofenac was administered to patients in all other countries.
ⁱ Cross-over trial; data presented have are sorted by the first intervention that the patients received in the trial.
^j Diclofenac and ibuprofen groups combined.

Rofecoxib

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (≤325 mg/day) (%)	Disease condition and other comments
Ehrich, 1999 ²²⁹ Multicentre, USA 6 weeks MSD Study 010	Rofecoxib 125 mg/day (125 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.) Placebo	74 73 72	63.9 64.0 62.6	59.5 80.8 73.6	11.3 12.0 12.2	100 100 100	0 0 0	Unclear but appear to be excluded	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Functional class: (I, II, III)
Laine, 1999 ³⁷ Multicentre, USA 24 weeks (12 weeks for primary outcome) MSD Study 044/045	Rofecoxib 50 mg/day (50 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.) Ibuprofen 2400 mg/day (800 mg t.d.s.) Placebo	186 195 183 177	62 62 62 61	69 69 66 66	NR NR NR NR	Overall 93	18 22 19 18	Low-dose aspirin not permitted	OA (location not stated) Included patients taking GPA (no; only antacids permitted) Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (yes) Patients positive for HP were included: placebo 28%; rofecoxib 25 mg 23%; rofecoxib 50 mg 30%; ibuprofen 27%. No information about whether this was treated at any stage
Cannon, 2000 ³⁰²³¹ Multicentre, USA 12 months MSD Study 035	Rofecoxib 12.5 mg/day (12.5 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.) Diclofenac 150 mg/day (50 mg t.d.s.)	259 257 268	62.8 62.8 62.5	65.3 68.1 69.0	11.1 11.5 11.4	92.7 92.6 90.3	NR NR NR (allowed but not reported)	Patients on aspirin were excluded	OA (hip, knee) Site(s) of OA: Hip: rofecoxib 12.5 mg 23.6%, rofecoxib 25 mg 26.5%, diclofenac 22.8%. Knee: rofecoxib 12.5 mg 76.4%, rofecoxib 25 mg 73.5%, diclofenac 77.2%. Included patients taking GPA (can't tell) Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Functional class (I, II, III)

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (≤325 mg/day) (%)	Disease condition and other comments
Day, 2000 ^{232,233} Multicentre, international 6 weeks MSD Study 040	Rofecoxib 12.5 mg/day (12.5 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.) Ibuprofen 2400 mg/day (800 mg t.d.s.) Placebo	244 242 249 74	64.9 62.8 64.1 63.1	81 79 78 85	8.3 8.5 9.0 9.3	91 87 92 91	NR NR NR NR	Patients requiring aspirin at any dose were excluded	OA (hip, knee) Proportions if more than one site: hip/knee OA: placebo 23/77%; rofecoxib 12.5 mg 22/78%, rofecoxib 25 mg 20/80%; ibuprofen 25/75%. Included patients taking GPA (can't tell) Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Functional class: (I, II, III)
Hawkey, 2000 ²³⁴ International (36 centres) 24 weeks (12 weeks for primary outcome) MSD Study 044/045	Rofecoxib 25 mg/day (25 mg o.d.) Rofecoxib 50 mg/day (50 mg o.d.) Ibuprofen 2400 mg/day (800 mg t.d.s.) Placebo	195 193 193 194	62 61 61 62	77 72 74 75	NR NR NR NR	Overall 49.4% patients had prior NSAIDs within 30 days of the start of the study	12 10 13 9	Aspirin not allowed	OA (location not stated) GPA allowed during the trial (no). Included patients on steroids (no) and/or anticoagulants (no). Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy: (yes) HP positive: placebo 58%, rofecoxib 25mg 57%, rofecoxib 50 mg 60%, ibuprofen 54%. Included functional class (can't tell)
Saag, 2000a ²³⁵ Multicentre, USA 6 weeks MSD Study 033	Placebo Rofecoxib 12.5 mg/day (12.5 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.) Ibuprofen 2400 mg/day (800 mg t.d.s.)	69 219 227 221	62 60 62 61	81.2 76.3 71.4 73.8	9 10 11 10	87 90.4 91.2 90.1	NR NR NR NR	Excluded from entry	OA (hip, knee) Proportions if more than one site: hip/knee: placebo 23/77%; rofecoxib 12.5 mg 22/78%; rofecoxib 25 mg 27/73%; ibuprofen 23/77%. Included patients taking GPA (no) Patients on regular antacids, PPIs and H2 blockers excluded. Included patients on anticoagulant (no) excluded. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy: presumably not tested

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Saag, 2000 ^{b,235} Multicentre, international 1 year MSD Study 034	Rofecoxib 12.5 mg/day (12.5 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.) Diclofenac 150 mg/day (50 mg t.d.s.)	231 232 230	62 62 63	81.0 77.7 81.7	8 9 9	88.7 89.7 89.1	NR NR NR	Excluded from entry	OA (hip, knee) Proportions if more than one site: hip/knee: rofecoxib 12.5 mg 18/82%; rofecoxib 25 mg 18/82%; diclofenac 20/80%. Included patients taking GPA (no) Patients on regular antacids, PPIs and H2 blockers excluded. Included patients on anticoagulant (no) excluded. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy: presumably not tested
Acevedo, 2001 ²³⁶ International (6 countries) 6 weeks MSD Study 902	Rofecoxib 12.5 mg/day (12.5 mg o.d.) Arthrotec (diclofenac 100 mg + misoprostol 400 µg/day) (diclofenac 50 mg + misoprostol 200 µg b.d.)	242 241	61.8 62.4	79.3 81.3	6.8 8.5	66.5 58.9	7.4 7.1	Excluded from entry	OA (location not stated) Inclusion: age at least 40 years with an established diagnosis of OA requiring regular NSAIDs. Exclusion: inflammatory or post-traumatic arthritis; GI disease; infectious diseases; malabsorption; uncontrolled diabetes or other serious medical conditions; bleeding disorder; faecal occult blood; previous use of misoprostol, regular use of aspirin, steroids in previous month, and sustained use of GI medication. Prior history of GI ulceration or bleed: rofecoxib = 7.4%, Arthrotec = 7.1%

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (≤ 325 mg/day) aspirin (%)	Disease condition and other comments
Ehrlich, 2001 ²³⁷⁻²⁴¹ Multicentre, USA 6 weeks MSD Study 029	Placebo	145	61.4	68.3	10.3	100	–	–	OA (hip, knee) Results section of this study states: "The efficacy results of rofecoxib in the management of OA from this study have been reported elsewhere (see Ehrlich EW, et al., 1999)". The numbers of patients between these 2 studies differ, also Ehrlich 1999 does not report data on rofecoxib 5 or 50 mg/day dose. Note Ehrlich et al. 1999 reported knee OA only, this study reports hip and knee OA data. Age >40 years. Hip and knee OA – note 50 mg dose 100% knee OA. History of benefit from NSAID required. Worsening of pain on cessation of NSAID required. Regular NSAID use 25 of 30 days prior to entry. Patients with creatinine clearance <30 ml/min, history of CV disease, previous peptic ulcer, GI bleeding, GI surgery, diabetes, previous stroke excluded (<2 years)
	Rofecoxib 5 mg/day (5 mg o.d.)	149	61.2	71.8	11.6	100			
	Rofecoxib 12.5 mg/day (12.5 mg o.d.)	144	61.4	71.5	11.4	100			
	Rofecoxib 25 mg/day (25 mg o.d.)	137	63.0	75.9	9.4	100			
Truitt, 2001 ²⁴² Multicentre, USA 6 weeks MSD Study 058	Rofecoxib 50 mg/day (50 mg o.d.)	97	61.3	66.0	12.0	100			
	Placebo	52	83.0	65.4	12.3	76.9	13.5	36.5	OA (hip, knee)
	Rofecoxib 12.5 mg/day (12.5 mg o.d.)	118	83.3	65.3	17	75.4	9.3	32.2	Proportions if more than one site: hip/ knee ratios: placebo 29/71%; rofecoxib 12.5 mg 29/71%; rofecoxib 25 mg 38/62%; nabumetone 32/68%.
	Rofecoxib 25 mg/day (25 mg o.d.)	56	83.8	57.1	14	76.8	17.9	41.1	Included patients taking GPA (can't tell) Antacid use placebo 35%; rofecoxib 12.5 mg 30%; rofecoxib 25 mg 41%; nabumetone 23%.
Nabumetone 1500 mg/day (1500 mg o.d.)	115	83.1	64.3	14.6	74.8	6.1	27.8	Included patients on anticoagulant (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy: presumably not tested	

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (≤325 mg/day) (%)	Disease condition and other comments
Myllykangas-Luosujärvi, 2002 ²⁴³	Rofecoxib 12.5 mg/day (12.5 mg o.d.)	471	61.9	80.3	Not reported	89.2	3.6	Proportion not reported	OA (knee, hip) Proportion of knee OA: rofecoxib 87.5%, naproxen 87.1%.
Multinational (2 identical RCTs combined) 6 weeks MSD Study 901	Naproxen 1000 mg/day (500 mg b.d.)	473	61.3	76.5		89.9 (chronic use)	4.4	Aspirin > 100 mg/day excluded	Included patients taking GPA (no) Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Niccoli, 2002 ²²⁸ Italy 2 weeks	Rofecoxib 25mg/day (25 mg o.d.)	30	72.42	60.0	CT	CT	-	-	OA (hand, hip, knee) Proportion: knee 41%, hip 22%, hand 37%.
	Diclofenac 150 mg/day (50 mg t.d.s.)	30	71.06	63.3					Included patients taking GPA (can't tell) Included patients on steroids (no) and/or anticoagulants (no)
	AMG 3600 mg/day (1200 mg t.d.s) plus 600 mg/day (600 mg o.d.)	30	73.27	60.0					Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Lisse, 2003 ²⁴⁴ ADVANTAGE study USA and Sweden 12 weeks MSD Study 102/903	Rofecoxib 25 mg/day (25 mg o.d.)	2785	63	71	Overall 92% had symptoms > 1 year	92	47	Overall 13% of patients on low-dose aspirin (< 100 mg). Patients on higher doses of aspirin not included	OA (knee, hand, hip, spine) Proportions if more than one site: Rofecoxib: knee 51%; hand 16%; hip 9%; spine 24%. Naproxen: knee 49%; hand 17%; hip 11%; spine 23%.
	Naproxen 1000 mg/day (500 mg b.d.)	2772	63	71		92	47		Included patients taking GPA (yes) Sustained use (>4 consecutive days) of PPI, H2-blockers or antacids not permitted at entry but allowed during study. Included patients on anticoagulant (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (≤ 325 mg/day) aspirin (%)	Disease condition and other comments
Kivitz, 2004 ¹⁶¹ USA 6 weeks MSD Study 085	Rofecoxib 12.5 mg/day (12.5 mg o.d.) Nabumetone 1000 mg/day (1000 mg o.d.) Placebo	424 410 208	63.6 62.2 64.1	68 70 67	6.4 5.9 6.1	96.5 93.7 95.7	18.6 18.5 15.9	10.8 13.9 10.1	OA Site(s) of OA and proportions if more than one site: knee 100% Included patients taking GPA (no) Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Schnitzer, 1999 ²⁴⁶ Multicentre, USA 8 weeks MSD Study 068	Placebo Rofecoxib 5 mg/day (5 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.) Rofecoxib 50 mg/day (50 mg o.d.)	168 158 171 161	54.7 54.8 55.7 54.4	72 75.9 78.9 80.7	8 11 9 10	100 100 100 100	NR NR NR NR	NR NR NR NR	RA Included patients taking GPA (can't tell) Included patients on steroids (yes) and/or anticoagulants (can't tell). Proportions on steroids: placebo 22.6%; rofecoxib 5 mg 22.8%; rofecoxib 25 mg 20.5%; rofecoxib 50 mg 22.4%. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) ACR functional class IV excluded. Proportions in other classes similar Entry: flare on withdrawal, usual NSAID necessary for entry, 35.8% of screened patients did not meet this criterion

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Bombardier, 2000 ^{39,44,66} International Median 9 months VIGOR study	Rofecoxib 50 mg/day (50 mg o.d.)	4047	58	79.6	10.9	82.1	7.7	0	RA Included patients taking GPA (yes) Details of the GPA allowed and proportions: Antacids and H2-blockers in specified doses (below prescription doses) were permitted. Patients on PPIs excluded. Included patients on steroids (yes) and/or anticoagulants (no) Proportions of patients on corticosteroids: rofecoxib 55.8%; naproxen 56.2%. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (yes). Rofecoxib 43.7% positive, naproxen 43.1% positive.
	Naproxen 1000 mg/day (500 mg o.d.)	4029	58	79.8	10.7	82.7	7.8	0	Included functional class (I, II, III, IV) Primary end-point was a composite of UGI PUB. This includes people without serious morbidity. Secondary end-point was upper GI perforations, obstructions or bleeds (equivalent to POB)
Geusens, 2002 ^{2,7} International multicentre 12 weeks MSD Study 097	Placebo	289	53.7	84.8	8.6	100	NR	0	RA Included patients taking GPA (can't tell) Included patients on steroids (yes) and/or anticoagulants (no)
	Rofecoxib 25 mg/day (25 mg o.d.)	306	52.9	80.1	8.2	100	NR	0	Corticosteroids: placebo 58.8%; rofecoxib 25 mg 58.5%; rofecoxib 50 mg 57.7%; naproxen 53.5%. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Presumably not tested.
	Rofecoxib 50 mg/day (50 mg o.d.)	286	53.7	83.9	8.6	100	NR	0	Patients in ACR functional class IV excluded
	Naproxen 1 g/day (500 mg b.d.)	142	54.1	82.4	9.1	100	NR	0	

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (≤325 mg/day) (%)	Disease condition and other comments
Hawkey, 2003 ²⁴⁸ International (18 countries) 12 weeks MSD Study 098/103	Rofecoxib 50 mg/day (50 mg o.d.) Naproxen 1000 mg/day (500 mg b.d.) Placebo	219 220 221	53 51 51	86 78 82	NR NR NR	68 57 70	11 14 10	Excluded from entry	RA Inclusion: Age 21–85 years with a confirmed clinical diagnosis of RA and a requirement for at least 3 months of NSAIDs. Exclusion: ulcer, pyloric obstruction or erosive oesophagitis at baseline endoscopy. Creatinine >2.0 mg/dl; creatinine clearance ≤30 ml/min; bleeding diathesis; anticoagulants; aspirin; ticlopidine, clopidogrel; unstable medical disease including angina, congestive heart failure, previous UGI surgery, faecal occult blood, inflammatory bowel disease, MI, coronary angioplasty, coronary bypass graft, cerebrovascular event, active hepatitis and history of malignancy within the previous 5 years. Non-study NSAIDs, antiseptory or cytoprotective drugs and steroids permitted at stable doses. Following prohibited: H2 antagonists, proton pump inhibitors, prostaglandin analogues, other gastroprotective agents, calcium antacids, anticoagulants, antiplatelet therapy and cyclosporin

^a Duration of follow-up.
^b Dose per day.
^c Number of randomised.
^d Values are means unless specified otherwise.
^e Prior GI ulcers unless specified otherwise.

Etoricoxib

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (≤325 mg/day) (%)	Disease condition and other comments
Gottesdiener, 2002 ^{250,251} Multicentre, USA 14 weeks (2 parts; only part 1 included) MSD Study 007	Part 1 (6 weeks) Etoricoxib 5 mg/day (5 mg o.d.) Etoricoxib 10 mg/day (10 mg o.d.) Etoricoxib 30 mg/day (30 mg o.d.) Etoricoxib 60 mg/day (60 mg o.d.) Etoricoxib 90 mg/day (90 mg o.d.) Placebo Part 2 (8 weeks) Etoricoxib 30 mg/day (30 mg o.d.) Etoricoxib 60 mg/day (60 mg o.d.) Etoricoxib 90 mg/day (90 mg o.d.) Diclofenac 150 mg/day (50 mg t.d.s)	117 114 102 112 112 60	61.74 62.47 61.25 60.03 60.10 62.52	76.9 77.2 65.7 66.1 67.9 78.3	7.39 8.60 8.86 7.60 7.16 7.18	100 100 100 100 100 100	NR (Allowed but not reported)	0 0 0 0 0 0 (Excluded)	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Included functional class I, II, III Part 2 not an RCT

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (≤325 mg/day) (%)	Disease condition and other comments
Leung, 2002 ²⁵² International 12 weeks MSD Study 019	Etoricoxib 60 mg/day (60 mg o.d.) Naproxen 1000 mg/day (500 mg b.d.) Placebo	224 221 56	62.9 63.2 64.1	77 78 82	5.9 6.3 6.3	95 90 93	NR NR NR	NR NR NR	OA (hip, knee) Proportions if more than one site: hip or knee OA patients included. Knee OA proportions: placebo 79%; etoricoxib 76%; naproxen 78%. Included patients taking GPA (yes) Details of the GPA allowed and proportions: Regular users of misoprostol (within 1 month of study), and regular users of PPI, H2 blockers excluded but were allowed (even at prescription doses) after randomisation. Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) – HP status probably not assessed
Hunt, 2003 ²⁵³ Multicentre, international 12 weeks MSD Study 029	Etoricoxib 120 mg/day (120 mg o.d.) Ibuprofen 2400 mg/day (800 mg t.d.s.) Placebo	221 226 233	61 62 62	76 69 77	NR NR NR	46 39 42	8 8 11	2 7 4	OA (location not stated) Included patients taking GPA (no) 2-week washout so all GPA discontinued before study entry. Antacid permitted during study. Included patients on anticoagulant (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (yes). HP positive: placebo 57%; etoricoxib 55%, ibuprofen 60% Baseline gastroduodenal erosions: placebo 20%; etoricoxib 15% ; ibuprofen 16%. Those with UGI ulcer, pyloric obstruction or erosive oesophagitis at baseline were excluded

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Zacher, 2003 ²⁵⁴ International (outside USA) 6 weeks MSD Study 805	Etoricoxib 60 mg/day (60 mg o.d.) Diclofenac 150 mg/day (50 mg t.d.s)	256 260	63.1 63.0	81.3 79.6	7.5 7.5	Data are separately given for II NSAIDs: see Table I, p. 730 in the paper	Not given	Aspirin > 100 mg Excluded. (aspirin < 100 mg, i.e. cardioprotective dosage allowed)	OA (knee, hip) Proportions if more than one site: knee (397/516) or hip (119/516) Included patients taking GPA (yes) Details of the GPA allowed and proportions: GPA allowed. Included patients on anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) ASA functional class (I, II, III)
Collantes, 2002 ²⁵⁵ Multicentre, international 12 weeks MSD Study 025	Etoricoxib 90 mg/day (90 mg o.d.) Naproxen 1000 mg/day (500 mg b.d.) Placebo	353 181 357	53 52 52	81 82 82	8 8 9	100 100 100	NR NR NR	Aspirin < 100 mg/day permitted – overall < 3% took aspirin	RA Included patients taking GPA (can't tell) Included patients on steroids (yes) and/or anticoagulants (no) Proportions of patients on steroids (prednisolone < 10 mg/day): placebo 57%; etoricoxib 54%; naproxen 59%. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Patients in ACR functional classes (I, II, III)
Matsumoto, 2002 ²⁵⁶ Multicentre, USA 12 weeks MSD Study 024	Etoricoxib 90 mg/day (90 mg o.d.) Naproxen 1000 mg/day (500 mg b.d.) Placebo	323 170 323	55 56 56	73 77 81	9 10 9	100 100 100	NR NR NR	Aspirin < 100 mg/day permitted – overall < 3% took aspirin	RA Included patients taking GPA (can't tell) Included patients on steroids (yes) and/or anticoagulants (no) Proportions of patients on steroids (prednisolone < 10 mg/day): placebo 32%; etoricoxib 29%; naproxen 34%. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Patients in ACR functional classes (I, II, III)

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (≤ 325 mg/day) aspirin (%)	Disease condition and other comments
Hunt, 2003b ²⁵⁷ USA and Canada 12 weeks MSD Study 026	Etoricoxib 120 mg/day (120 mg o.d.) Naproxen 1000 mg/day (500 mg b.d.) Placebo	251 244 247	53 54 54	84 83 81	NR NR NR	74 77 72	10 9 9	4 5 4	RA or OA (location not stated) Included patients taking GPA (no) Included patients on steroids (yes) and/or anticoagulants (can't tell). Proportions of patients on corticosteroids: etoricoxib 37%, naproxen 37%, placebo 39%. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (yes) % HP positive: etoricoxib 51%, naproxen 58%, placebo 60% Functional class (can't tell) OA patients: etoricoxib 27%, naproxen 23%, placebo 24%
^a Duration of follow-up. ^b Dose per day. ^c Number of randomised. ^d Values are means unless specified otherwise. ^e Prior GI ulcers unless specified otherwise.									

Valdecoxib

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Fiechter, 2001 ^{258,268} 6 weeks Pfizer Study 015	Valdecoxib 1 mg/day (0.5 mg b.d.) Valdecoxib 2.5 mg/day (1.25 mg b.d.) Valdecoxib 5 mg/day (2.5 mg b.d.) Valdecoxib 10 mg/day (5 mg b.d.) Valdecoxib 10 mg/day (10 mg o.d.) Valdecoxib 20 mg/day (10 mg b.d.) Naproxen 1000 mg/day (500 mg b.d.) Placebo		[Confidential information removed]						
Kivitz, 2002 ²⁵⁹ US and Canada (85 centres) 12 weeks Pfizer Study 053	Valdecoxib 5 mg/day (5 mg o.d.) Valdecoxib 10 mg/day (10 mg o.d.) Valdecoxib 20 mg/day (20 mg o.d.) Naproxen 1000 mg/day (500 mg b.d.) Placebo	201 206 202 205 205	58.7 59.8 59.6 60.4 60.3	64 65 67 63 64	9.8 8.7 9.2 9.4 8.3	NR NR NR NR NR	10 12 14 15 10	May be allowed but not clearly reported	OA (knee) Included patients taking GPA: (no) Included patients on steroids (no) and/or anticoagulants (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Included functional class (can't tell)

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Maikarowski, 2002 ²⁶⁰ USA and Canada 12 weeks Pfizer Study 049	Valdecoxib 5 mg/day (5 mg o.d.) Valdecoxib 10 mg/day (10 mg o.d.) Naproxen 1000 mg/day (500 mg b.d.) Placebo	120 111 118 118	60.4 63.9 63.1 62.1	67 66 69 69	6.4 6.5 5.3 6.2	NR NR NR NR	8 13 9 11	Allowed but % not reported	OA (hip) Included patients taking GPA: (can't tell) and included patients on steroids (can't tell) and anticoagulant (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Functional class: (can't tell)
Sikes, 2002 ²⁶¹ USA and Canada 12 weeks Pfizer Study 048	Valdecoxib 10 mg/day (10 mg o.d.) Valdecoxib 20 mg/day (20 mg o.d.) Ibuprofen 2400 mg/day (800 mg t.d.s.) Diclofenac SR 150 mg/day (75 mg b.d.) Placebo	204 219 207 212 210	58.6 60.1 60.2 61.1 59.5	66 70 67 69 69	9.8 11.9 9.9 10.8 9.4	Not reported (but requiring chronic use of NSAIDs and/or oral analgesics was an inclusion criteria)	13 14 14 15 11	9–18% across treatment groups	OA (location not stated) Included patients taking GPA: (no) Included patients on anticoagulant (no). Included patients with positive <i>H. pylori</i> (HP) status (yes) and/or on HP therapy (no). HP positive: placebo 37%, valdecoxib 10 mg 30%, 20 mg 46%, ibuprofen 43%, diclofenac 40% (significant difference between groups) Functional class: (can't tell)
Moskowitz, 2003 ^{245,286} 2 weeks Pfizer Study 143	Valdecoxib 10 mg/day (10 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.) Placebo	212 208 110	[Confidential information removed]						
Pfizer Study 063 (Pfizer 2004 submission)	[Confidential information removed]								

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Pfizer Study 047 [Confidential information removed] (Pfizer 2004 submission)									
Bensen, 2002 ²⁶⁴ Canada and USA 12 weeks	Valdecoxib 10 mg/day (10 mg o.d.)	209	55.3	75	10.0	100	8.1	Permitted but proportions not reported	RA Included patients taking GPA: (can't tell) Included patients on steroids (can't tell) and/or anticoagulants (no). Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Included functional class: (I, II)
Pfizer Study 60	Valdecoxib 20 mg/day (20 mg o.d.)	212	55.3	71	10.0	100	9.4		
	Valdecoxib 40 mg/day (40 mg o.d.)	221	54.9	79	9.4	100	8.1		
	Naproxen 1000 mg/day (500 mg b.d.)	226	55.4	81	9.9	100	8.0		
	Placebo	222	55.7	77	10.3	100	8.1		
Pavelka, 2003 ²⁶⁵ International, 26 weeks Pfizer Study 062									
	Valdecoxib 20 mg/day (20 mg o.d.)	246	55.7	73	9.9	Not reported	10.6	5.7	RA Included patients taking GPA: (can't tell) Included patients on steroids (yes) and/or anticoagulants (yes). Proportions of patients on these drugs: not reported. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (yes). Proportions positive: valdecoxib 20 mg 38.6%; valdecoxib 40 mg 37.1%; diclofenac 36%. Included functional class (I, II, III)
	Valdecoxib 40 mg/day (40 mg o.d.)	237	54.8	71	10.6		5.9	5.9	
	Diclofenac SR 150 mg/day (75 mg b.d.)	239	56.4	80	10.0		5.9	5.4	
Pfizer 016 ²⁶⁶ (Pfizer 2004 submission)									
[Confidential information removed]									
Pfizer 061 ²⁶⁷ (Pfizer 2004 submission)									
[Confidential information removed]									

^a Duration of follow-up.^b Dose per day.^c Number of randomised.^d Values are means unless specified otherwise.^e Prior GI ulcers unless specified otherwise.

Lumiracoxib

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (\leq 325 mg/day) aspirin (%)	Disease condition and other comments
Schnitzer, 2004 ^{270,438} Multinational 4 weeks Novartis Study 0104	Lumiracoxib 100 mg/day (50 mg b.d.) Lumiracoxib 200 mg/day (100 mg b.d.) Lumiracoxib 400 mg/day (200 mg b.d.) Lumiracoxib 400 mg/day (400 mg o.d.) Diclofenac 75 mg/day b.d. Placebo	98 96 99 99 94 97	61.3 59.8 59.5 60.1 59.7 61.5	68 70 75 59 68 67	7.4 6.6 6.9 6.3 6.3 8.0	NR NR NR NR NR NR	NR NR NR NR NR NR	NR NR NR NR NR NR	OA (of hip or knee) GPA allowed in during the trial (no) Included patients on steroids (no) and/or anticoagulants (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Included functional class (can't tell)
Hawkey, 2004 ^{207,287} Multinational 13 weeks Novartis Study 0126	Lumiracoxib 200 mg/day (200 mg o.d.) Lumiracoxib 400 mg/day (400 mg o.d.) Celecoxib 200 mg/day (200 mg o.d.) Ibuprofen 2400 mg/day (800 mg t.d.s.)	264 260 258 260	58.8 58.1 59.9 57.9	79.2 74.6 76.7 76.2	8.0 7.6 8.1 6.9	81.4 81.9 82.9 86.2	5.3 7.7 4.3 5.8	NR NR NR NR	OA (hip, knee or hand) GPA allowed in during the trial (no) Included patients on steroids (yes) and/or anticoagulants (no). Proportions of patients on these drugs: low-dose corticosteroids 1.1, 0.0, 0.8, 0.8 for lumiracoxib 200 mg, 400 mg, ibuprofen and celecoxib groups, respectively. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (yes) Included functional class (I, II, III)

continued

Author/trial name, year, country, duration ^d	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Benevolenskaya, 2003 ^{271,441} Multinational 4 weeks Novartis Study 2316	[Confidential information removed]								
Fleischmann, 2003 ^{208,209} Multinational 13 weeks Novartis Study 0109	Lumiracoxib 200 mg/day (200 mg o.d.) Lumiracoxib 400 mg/day (400 mg o.d.) Celecoxib 200 mg/day (200 mg o.d.) Placebo		[Confidential information removed]						OA (knee) [Confidential information removed]
Grifka, 2003 ^{272,442} Multinational 4 weeks Novartis Study 2319	[Confidential information removed]								
Tannenbaum, 2004 ²¹⁰ International, multicentre 13 weeks Novartis Study 0112	Lumiracoxib 200 mg/day (200 mg o.d.) Lumiracoxib 400 mg/day (400 mg o.d.) Celecoxib 200 mg/day (200 mg o.d.) Placebo	487 491 481 243	64.1 64.3 64.1 64.6	69.6 67.4 69.2 67.1	4.2 5.2 5.3 4.3	NR NR NR NR	[Confidential information removed]	[Confidential information removed]	OA of the knee Included patients taking GPA (no) Included patients on steroid (no) and anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Inclusion: pain intensity \geq 40 mm on 100 mm VAS at the end of washout; but no flare required. Paracetamol \leq 2 g/day and low-dose aspirin \leq 325 mg/day permitted

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (≤ 325 mg/day) aspirin (%)	Disease condition and other comments
Novartis Study 0128 Multinational [Confidential information removed]	[Confidential information removed]								
Novartis Study 2307 Multinational [Confidential information removed]	[Confidential information removed]								
TARGET trial Novartis Studies 0117 (vs naproxen) and Study 2332 (vs ibuprofen) International 52 weeks ²⁷³⁻²⁷⁵	Lumiracoxib 400 mg/day (400 mg o.d.) Naproxen 1000 mg/day (500 mg b.d.) Ibuprofen 2400 mg/day (800 mg t.d.s.)	9156 4754 4415	63.5 63.6 63.3	76.4 76.6 76.1	5.7 5.7 5.4	76.7 73.7 80.0	2.9 3.5 3.5	23.8 25.2 22.0	OA of hip, knee, hand, cervical or lumbar spine and symptoms for > 3 months. More than 50% in each group knee disease. Included patients taking GPA (no, not permitted except as rescue medication). Included patients on steroids: (yes) Proportion of patients on steroids: Lumiracoxib 9.5%, naproxen 8.2%, ibuprofen 9.5%. Included patients on anticoagulant (no). Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (yes). Lumiracoxib 44.2%, naproxen 46.9%, ibuprofen 41.1%.
						Regular use in past 6 months		(Patients were stratified for aspirin use)	Stratification according to age: age <65, 65-74, > 74 years. Patients also stratified according to aspirin use

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (\leq 325 mg/day) aspirin (%)	Disease condition and other comments
[Confidential information removed]									
Giesens, 2003 ^{276,443} Multinational 26 weeks Novartis Study 0111 [Confidential information removed]									
Kivitz, 2004 ²¹⁴ Multinational 13 weeks Novartis Study 0110	Lumiracoxib 400 mg/day (400 mg o.d.) Lumiracoxib 800 mg/day (800 mg o.d.) Celecoxib 400 mg/day (200 mg b.d.) Ibuprofen 2400 mg/day (800 mg t.d.s.)	227	52.4	78.0	7.8	96.9	NR	NR	RA GPA allowed in during the trial (no) Included patients on steroids (yes) and/or anticoagulants (no). Proportions of patients on these drugs: low-dose corticosteroids 3.1, 3.1, 1.8, 0.9 for lumiracoxib 400 mg, 800 mg, celecoxib 200 mg and placebo groups, respectively. Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (yes) Included functional class (I, II or III)
[Confidential information removed]									
Scott, 2003 ^{277,281} Novartis Study 2312 [Confidential information removed]									
Novartis Study 0105 ²⁷⁹ [Confidential information removed]									

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose (\leq 325 mg/day) aspirin (%)	Disease condition and other comments
Novartis Study 0114 ²²² [Confidential information removed]	[Confidential information removed]								
Novartis A2335 ²⁷⁸ [Confidential information removed]	[Confidential information removed]								

^a Duration of follow-up.
^b Dose per day.
^c Number of randomised.
^d Values are means unless specified otherwise.
^e Prior GI ulcers unless specified otherwise.

Head-to-head trials

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
McKenna, 2001 ^{b,197} USA 20 centres 6-weeks Pfizer Study 152	Celecoxib 200 mg/day (200 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.) Placebo	63	62	67	11.2	71	10	NR	OA (knee) Included patients taking GPA (no) Included patients on steroids (can't tell) Included patients <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) HP therapy not allowed Included functional class (I, II, III)
Whelton, 2001 ^{282,283} SUCCESS VI USA and Canada (101 centres) 6 weeks Pfizer Study 149	Celecoxib 200 mg/day (200 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.)	411	74.0	66.5	13.6	NR	NR	37.9	OA (hip, knee, hand) Inclusion: Age > 65 years; stable controlled hypertension and a diagnosis of OA (according to American College of Rheumatology criteria) of hip/knee/hand. Also needed chronic daily therapy with NSAIDs Exclusion: active GI disease; renal, hepatic or coagulation disorders; history of New York Heart Association class III or IV heart failure; secondary or malignant hypertension; renal artery stenosis; acute joint trauma; RA; active crystal arthropathies; history of ulcer within 30 days of trial start; or recent (<30 days) use of celecoxib or rofecoxib. Serum creatinine > 132.6 µmol/l, high blood urea nitrogen levels and low or high potassium level Aspirin use allowed during trial, but not other NSAIDs, steroids or antiulcer drugs
		399	74.1	66.4	11.7	NR	NR	37.1	

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Whelton, 2002a ²⁸⁴ SUCCESS VII USA and Canada 6 weeks Pfizer Study 181	Celecoxib 200 mg/day (200 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.)	549	73.3	63.9	11.7	NR	NR	NR	OA (hip, knee, hand) Proportions not reported. Included patients taking GPA (can't tell) Included patients on anticoagulant (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell). No indication that this was tested This study compares half of the maximum permitted dose of celecoxib (400 mg) for OA versus the full permitted dose of rofecoxib (25 mg)
Gibofsky, 2003 ²⁰² US and Canada 6 weeks Pfizer Study 003	Celecoxib 200 mg/day (200 mg o.d.) Rofecoxib 25 mg/day (25mg o.d.) Placebo	189	62.2	69	8.6	Reported "similar across all three groups"	6	NR	OA (knee) Inclusion: ≥40-year-olds with OA of the knee (by ACR criteria), with functional capacity class rating of I, II and III, OA in a flare and negative pregnancy test. Exclusion: inflammatory arthritis, acute joint trauma in index knee, recent steroids or hyaluronic acid injection, NSAID use (with the exception of low-dose aspirin) within the previous 2 days or 5 half-lives of the drug, active or history of malignancy, UGI ulceration, active GI disease, chronic or acute renal or hepatic disorder, coagulation defect, allergy to NSAIDs and COX-2 inhibitors, abnormal laboratory tests
Sowers, 2003 ^{206,249} Pfizer Study 002 CRESCENT [Confidential information removed] 12 weeks	Celecoxib 200 mg/day (200 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.) Naproxen 1000 mg/day (500 mg b.d.)	136	[Confidential information removed]						

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Geba, 2002 ²⁸⁵ VACT-1 USA 6 weeks	Paracetamol 4 g/day (1 g q.d.s.) Celecoxib 200 mg/day (200 mg o.d.) Rofecoxib 12.5 mg/day (12.5 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.)	94 97 96 95	63.1 62.6 63.4 61.3	70.2 64.9 65.6 72.6	>0.5 >0.5 >0.5 >0.5	76.6 79.4 75 76.8	NR NR NR NR	NR NR NR NR	OA (knee) Included patients taking GPA (can't tell) Included patients on anticoagulant (can't tell) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell)
Moskowitz, 2003 ^{245,286} Multicentre 2 weeks Pfizer Study 143	Valdecoxib 10 mg/day (10 mg o.d.) Rofecoxib 25 mg/day (25 mg o.d.) Placebo	212 208 110	[Confidential information removed]						
Hawkey, 2004 ^{207,287} Multinational, 13 weeks Novartis Study 0126	Lumiracoxib 200 mg/day (200 mg o.d.) Lumiracoxib 400 mg/day (400 mg o.d.) Celecoxib 200 mg/day (200 mg o.d.) Ibuprofen 2400 mg/day (800 mg t.d.s.)	264 260 258 260	58.8 58.1 59.9 57.9	79.2 74.6 76.7 76.2	8.0 7.6 8.1 6.9	81.4 81.9 82.9 86.2	5.3 7.7 4.3 5.8	NR	OA (hip, knee or hand) GPA allowed in during the trial (no) Included patients on steroids (yes) and/or anticoagulants (no). Proportions of patients on these drugs: low-dose corticosteroids 1.1, 0.0, 0.8, 0.8 for lumiracoxib 200 mg, 400 mg, ibuprofen and celecoxib groups, respectively Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (yes) Included functional class (I, II, III)

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Fleischmann, 2003 ^{208,209} Multinational 13 weeks Novartis Study 0109	Lumiracoxib 200 mg/day (200 mg o.d.) Lumiracoxib 400 mg/day (400 mg o.d.) Celecoxib 200 mg/day (200 mg o.d.) Placebo								OA (knee) [Confidential information removed]
Novartis Study 0128 ²⁸⁰ Multinational [Confidential information removed]	[Confidential information removed]								
Novartis Study 2307 ²⁸⁸ Multinational [Confidential information removed]	[Confidential information removed]								
Tannenbaum, 2004 ²¹⁰ International multicentre 13 weeks Novartis Study 0112	Lumiracoxib 200 mg/day (200 mg o.d.) Lumiracoxib 400 mg/day (400 mg o.d.) Celecoxib 200 mg/day (200 mg o.d.) Placebo	487 491 481 243	64.1 64.3 64.1 64.6	69.6 67.4 69.2 67.1	4.2 5.2 5.3 4.3	NR NR NR NR	[Confidential information removed]	[Confidential information removed]	OA of the knee Included patients taking GPA (no) Included patients on steroid (no) and anticoagulant (no) Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (can't tell) Inclusion: pain intensity ≥ 40 mm on 100 mm VAS at the end of washout, but no flare required Paracetamol ≤ 2 g/day and low-dose aspirin ≤ 325 mg/day permitted

continued

Author/trial name, year, country, duration ^a	Intervention and comparator ^b	N ^c	Age (years) ^d	Female (%)	Disease duration (years) ^d	Prior NSAIDs (%)	Prior GI events (%) ^e	Concurrent low-dose aspirin (%)	Disease condition and other comments
Kivitz, 2004 ^{2,14} Multinational 13 weeks	Lumiracoxib 400 mg/day (400 mg o.d.)	227	52.4	78.0	7.8	96.9	NR	NR	RA GPA allowed in during the trial (no) Included patients on steroids (yes) and/or anticoagulants (no). Proportions of patients on these drugs: low-dose corticosteroids 3.1, 3.1, 1.8, 0.9 for lumiracoxib 400 mg, 800 mg, celecoxib 200 mg and placebo groups, respectively
Novartis Study 0110	Lumiracoxib 800 mg/day (800 mg o.d.)	227	50.6	80.6	7.9	93.4			Included patients with positive <i>H. pylori</i> (HP) status and/or on HP therapy (yes)
	Celecoxib 400 mg/day (200 mg b.d.)	223	51.7	77.6	7.4	91.0			Included functional class (I, II or III)
	Ibuprofen 2400 mg/day (800 mg t.d.s)	216	52.2	79.6	8.6	93.5			
Novartis Study 0114 [Confidential information removed]	[Confidential information removed]								

^a Duration of follow-up.^b Dose per day.^c Number of randomised.^d Values are means unless specified otherwise.^e Prior GI ulcers unless specified otherwise.

Appendix 7

Quality assessment of included randomised controlled trials

Drug	Author, year, trial name	Appropriate method of randomisation	Adequate concealment	Double blind	ITT analysis	Loss to follow-up reported	Total Jadad score/5
Etodolac	Bacon, 1990a ^{136,137}	CT	CT	Y	N	CT	?2 – not enough detail in overview or interim papers
	Bacon, 1990b ^{136,137}	CT	CT	Y	N	CT	?2 – not enough detail in overview or interim papers
	Bacon, 1990c ^{136,137}	CT	CT	Y	N	CT	?2 – not enough detail in overview or interim papers
	Williams, 1989 ¹³⁸	CT	CT	Y	N	Y	3
	Freitas, 1990 ¹³⁹	CT	CT	Y	N	CT	4
	Astorga Paulsen, 1991 ¹⁴³	CT	CT	CT	N	Y	3
	Brasseur, 1991 ¹⁴⁰	CT	CT	Y	N	Y	4
	Karbowski, 1991 ¹⁴¹	CT	CT	Y	N	Y	3
	Palferman, 1991 ¹⁴²	CT	CT	Y?	N	Y	4
	Pena, 1991 ¹⁴⁴	CT	CT	CT	N	Y	3
	Perpignano, 1991 ¹⁴⁵	Y?	CT	Y	N/Y (tolerability)	Y	4?
	Dick, 1992 ¹⁴⁶	Y	CT	Y	CT	Y	3
	Grisanti, 1992 ¹⁴⁷	CT	CT	Y	N	CT	3
	Waterworth, 1992 ¹⁴⁸	CT	CT	Y	CT	Y	3
	Burssens, 1993 ¹⁴⁹	CT	CT	Y	Y	Y	2
	Eisenkolb, 1993 ¹⁵⁰	Y	CT	Y	CT	Y	3
	Chikanza, 1994 ¹⁵¹	CT	Y	Y	Y	Y	4
	Lucker, 1994 ¹⁵²	Y	Y	Y	N	CT	5
	Perpignano, 1994 ¹⁵³	Y	Y (distance randomisation)	Y	Y (partly)	Y	5
	Dore, 1995 ¹⁵⁴	CT	Y	Y	Y	CT	4
Schnitzer, 1995 ¹⁵⁵	CT	CT	Y	Y	Y	4	
Jennings, 1997 ¹⁵⁶	CT	CT	CT	N	N	2	

continued

Drug	Author, year, trial name	Appropriate method of randomisation	Adequate concealment	Double blind	ITT analysis	Loss to follow-up reported	Total Jadad score/5
	Rogind, 1997 ¹⁵⁷	CT	CT	Y	N	Y	4
	Schnitzer, 1997 ¹⁵⁸	CT	CT	Y	Y	Y	4
	Taha, 1989 ^{159,160}	CT	CT	Y	N	CT	2
	Delcambre, 1990 ³³⁹	CT	CT	Y	Y (Partly)	CT	4?
	Taha, 1990 ^{160,162}	CT	CT	Y	N	CT	2
	Lightfoot, 1997 ¹⁶³	Y	CT	Y	N	CT	4?
	Neustadt, 1997 ¹⁶⁴	Y	CT	Y	CT	CT	3
Meloxicam	Carrabba, 1995 ^{168,169}	CT	CT	N	Y	Y	1
	Hosie, 1996 ¹⁷⁰	CT	CT	Y	Y	N	3
	Linden, 1996 ¹⁶⁵	CT	CT	CT	Y	CT	3
	Goei The, 1997	CT	CT	Y	Y	CT	2
	Hosie, 1997 ¹⁷¹	CT	CT	Y	Y	CT	3
	Dequeker, 1998 ¹⁷² SELECT	CT	CT	Y	Y	CT	3+, not sufficient detail in paper
	Hawkey, 1998 ¹⁷³	CT	CT	Y	Y	Y	3+, not enough info. in paper
	Lund, 1998 ^{174,175}	CT	CT	Y	Y	CT	3
	Yocum, 2000 ¹⁷⁶⁻¹⁷⁸	CT	CT	Y	Y	CT	3
	Chang, 2001 ¹⁷⁹	CT	CT	Y	Y	Y	4
	Valat, 2001 ¹⁸⁰	CT	CT	Y	Y	Y	4
	Xu, 2002a ¹⁸¹	Y	CT	Y	N	Y	5
	Wojtulewski, 1996 ^{182,183}	CT	CT	Y	Y	N	4?
	Lemmel, 1997 ^{184,185}	CT	CT	Y	Y	N	3
	Furst, 2002 ^{167,186}	Y	CT	Y	Y	N	4
	Xu 2002b ^{187,188}	Y	CT	Y	N	CT	4
Celecoxib	Simon, 1998a ¹⁹⁰	Y	CT	Y	Y	N	3
	Bensen, 1999 ¹⁹¹⁻¹⁹³	CT	Y	Y	Y	CT	5?
	Williams, 2000 ¹⁹⁴	Y	CT	Y	Y	Y	5
	Goldstein, 2001b ^{195,224} (Pfizer 2004 submission)	Y	Y	Y	Y	Y	5

continued

Drug	Author, year, trial name	Appropriate method of randomisation	Adequate concealment	Double blind	ITT analysis	Loss to follow-up reported	Total Jadad score/5
	Kivitz, 2001 ¹⁹⁶	CT	Y (block randomisation)	Y	Y	Y	3
	McKenna, 2001b ¹⁹⁷	Y	CT	Y	Y	Y	5
	McKenna, 2001a ¹⁹⁸	CT	CT	Y	Y	Y	3
	Pfizer Study 021 (2000 submission) ²²¹	Y	CT	Y	Y	Y	5
	McKenna, 2002 ¹⁹⁹	Y	CT	Y	CT	CT	3
	Pfizer Study 047 (2000 submission) ⁴⁴⁴	Y	CT	Y	Y	Y	5
	Williams, 2001 ²⁰⁰	CT	CT	Y	Y	Y	5
	Suarez-Otero, 2002 ²⁰¹	N	N	Y	CT	CT	3
	Gibofsky, 2003 ²⁰²	Y	Y	Y	Y	Y	5
	Hawel, 2003 ²⁰³	CT	CT	Y	Y	CT	4
	Pincus, 2004 ^{204,205} PACESa	CT	CT	N	Y	CT	1
	Sowers, 2003 ^{206,249}	Y	Y	Y	Y	Y	5
	Pincus, 2004 ²⁰⁴ PACESb	CT	CT	N	Y	CT	1
	Pfizer Study 209 (2004 submission) ⁴³⁹	Y	Y	Y	Y	Y	5
	Pfizer Study 210 (2004 submission) ⁴⁴⁰	Y	Y	Y	Y	Y	5
	Pfizer Study 211 (2004 submission) ²²⁵	Y	Y	Y	Y	Y	5
	Pfizer Study 216 (2004 submission) ²²³	Y	Y	Y	Y	Y	5
	Hawkey, 2004 ^{207,287} Novartis Study 0126	Y	Y	Y	Y	Y	5
	Fleischmann, 2003 ^{208,209} Novartis Study 0109	Y	Y	Y	Y	Y	5

continued

Drug	Author, year, trial name	Appropriate method of randomisation	Adequate concealment	Double blind	ITT analysis	Loss to follow-up reported	Total Jadad score/5
	Tannenbaum, 2004 ²¹⁰ Novartis Study 0112	Y	CT	Y	Y	Y	5
	Simon, 1998b ¹⁹⁰	Y	CT	Y	Y	N	3
	Emery, 1999 ²¹¹	Y	CT	Y	Y	Y	5
	Simon, 1999 ^{212,213}	Y	Y	Y	Y	Y	5
	Pfizer Study 023 (2000 submission) ²²⁷	Y	Y	Y	Y	Y	5
	Kivitz, 2004 ²¹⁴ Novartis Study 0110	CT	CT	Y	Y	Y	4
	Novartis Study 0114 ²²²	Y	Y	Y	Y	Y	5
	Silverstein, 2000 ^{50,54,215-219} CLASS study	Y	Y	Y	Y	Y	5
	Goldstein, 2001 ^{220,269}	CT	CT	Y	Y	Y	5
	Pfizer Study 071 (2000 submission) ²²⁶	Y	Y	Y	Y	Y	5
	Chan, 2002 ⁵⁹	Y	Y	Y	Y	Y	5
	Pfizer Study 105 (2004 submission) ⁴⁴⁵	Y	Y	Y	Y	Y	5
	Pfizer Study 106 (2004 submission) ⁴⁴⁶	Y	Y	Y	Y	Y	5
	Pfizer Study 107 (2004 submission) ⁴⁴⁷	Y	Y	Y	Y	Y	5
Rofecoxib	Ehrich, 1999 ²²⁹	Y	Y	Y	Y	Y	5
	Laine, 1999 ³⁷	Y	Y	Y	Y	Y	5
	Cannon, 2000 ^{230,231}	Y	Y/CT?	Y	CT	Y	5
	Day, 2000 ^{232,233}	Y	Y	Y	Y	Y	5
	Hawkey, 2000 ²³⁴	Y	CT	Y	Y	Y	5
	Saag, 2000a ²³⁵	Y	Y	Y	Y	Y	5
	Saag, 2000b ²³⁵	Y	Y	Y	Y	Y	5
	Acevedo, 2001 ²³⁶	Y	CT	Y	Y	Y	5
	Ehrich, 2001 ^{237-239,240}	CT	CT	Y	Y	Y	3
	Truitt, 2001a ²⁴²	Y	Y	Y	Y	Y	5

continued

Drug	Author, year, trial name	Appropriate method of randomisation	Adequate concealment	Double blind	ITT analysis	Loss to follow-up reported	Total Jadad score/5
	Myllykangas-Luosujärvi, 2002 ²⁴³	Y	Y	Y	Y	Y	5
	Niccoli, 2002 ²²⁸	Y	CT	N	N	N	1
	Lisse, 2003 ²⁴⁴	Y	Y	Y	Y	Y	5
	Kivitz, 2004 ¹⁶¹	Y	Y	Y	Y	Y	5
	Schnitzer, 1999 ²⁴⁶	Y	CT	Y	Y	Y	5
	Bombardier, 2000 ^{39,44,66}	Y	Y	Y	Y	Y	5
	VIGOR Study						
	Geusens, 2002 ²⁴⁷	Y	CT	Y	Y	CT	4
	Hawkey, 2003 ²⁴⁸	Y	CT	Y	Y	Y	5
	McKenna, 2001b ¹⁹⁷	Y	CT	Y	Y	Y	5
	Gibofsky, 2003 ²⁰²	Y	Y	Y	Y	Y	5
	Sowers, 2003 ^{206,249}	Y	Y	Y	Y	Y	5
	Moskowitz, 2003 ^{245,286}	Y	Y	Y	Y	Y	5
	Novartis Study 0128 ²⁸⁰	Y	Y	Y	Y	Y	5
Etoricoxib	Gottesdiener, 2002 ^{250,251} (Part I)	Y	Y	Y	Y	Y	5
	Leung, 2002 ²⁵²	Y	Y	Y	CT	Y	5
	Hunt, 2003a ²⁵³	CT	CT	CT	CT	Y	3
	Zacher, 2003 ²⁵⁴	Y	Y	Y	Y	CT	4
	Collantes, 2002 ²⁵⁵	CT	CT	Y	CT	CT	3
	Matsumoto, 2002 ²⁵⁶	CT	CT	Y	Y	CT	3
	Hunt, 2003b ²⁵⁷	Y	Y	Y	Y	Y	5
Valdecoxib	Fiechtner, 2001 ^{258,268}	Y	CT	Y	Y	Y	5
	Kivitz, 2002 ²⁵⁹	Y	Y	Y	Y	Y	5
	Makarowski, 2002 ²⁶⁰	CT	CT	Y	Y	Y	3+
	Sikes, 2002 ²⁶¹	Y	CT	Y	Y	Y	4
	Moskowitz, 2003 ^{245,286}	Y	Y	Y	Y	Y	5
	Pfizer Study 063 ²⁶²	Y	Y?	Y	Y	Y	5
	Pfizer Study 047 ²⁶³	Y	Y	Y	Y	Y	5
	Bensen, 2002 ²⁶⁴	CT	CT	Y	Y	Y	3+, details not reported

continued

Drug	Author, year, trial name	Appropriate method of randomisation	Adequate concealment	Double blind	ITT analysis	Loss to follow-up reported	Total Jadad score/5
Lumiracoxib	Pavelka, 2003 ²⁶⁵	Y	Y/CT?	Y	Y	Y	5
	Pfizer Study 016 ²⁶⁶	Y	CT	Y	Y	Y	5
	Pfizer Study 061 ²⁶⁷	Y	CT	Y	Y	Y	5
	Schnitzer, 2004 ^{270,438}	CT	CT	Y	Y	Y	4
	Novartis Study 0104						
	Hawkey, 2004 ^{207,287}	Y	Y	Y	Y	Y	5
	Novartis Study 0126						
	Benevolenskaya, 2003 ^{271,441}	Y	Y	Y	Y	Y	5
	Novartis Study 2316						
	Fleischmann, 2003 ^{208,209}	Y	Y	Y	Y	Y	5
	Novartis Study 0109						
	Grifka, 2003 ^{272,442}	CT	CT	Y	Y	Y	4
	Novartis Study 2319						
	Tannenbaum, 2004 ²¹⁰	Y	CT	Y	Y	Y	5
	Novartis Study 0112						
	Novartis Study 0128 ²⁸⁰	Y	Y	Y	Y	Y	5
	Novartis Study 2307 ²⁸⁸	Y	Y	Y	Y	Y	5
TARGET, Novartis Study 0117/A2332 ²⁷³⁻²⁷⁵	Y	Y	Y	Y	Y	5	
Geusens, 2003 ^{276,443}	CT	CT	Y	Y	Y	4	
Novartis Study 0111							
Kivitz, 2004 ²¹⁴	CT	CT	Y	Y	Y	4	
Novartis Study 0110							
Scott, 2003 ^{277,281}	Y	Y	Y	Y	Y	5	
Novartis Study 2312							
Novartis Study 0105 ²⁷⁹	Y	Y	Y	Y	Y	5	
Novartis Study 0114 ²²²	Y	Y	Y	Y	Y	5	
Novartis Study A2335 ²⁷⁸	Y	Y	Y	Y	Y	5	

continued

Drug	Author, year, trial name	Appropriate method of randomisation	Adequate concealment	Double blind	ITT analysis	Loss to follow-up reported	Total Jadad score/5
Head-to-head	McKenna, 2001b ¹⁹⁷ Pfizer Study 152	Y	Y	Y	Y	Y	5
	Whelton, 2001 ^{282,283} Pfizer Study 149	Y	Y	Y	Y	Y	5
	Whelton, 2002a ²⁸⁴ Pfizer Study 181	Y	Y	Y	Y	Y	5
	Gibofsky, 2003, ²⁰² Pfizer Study 003	Y	Y	Y	Y	Y	5
	Sowers, 2003 ^{206,249} Pfizer 002	Y	Y	Y	Y	Y	5
	Geba, 2002 ²⁸⁵ VACT-1	Y	Y	Y	Y	Y	5
	Moskowitz, 2003 ^{245,286} Pfizer Study 143	Y	Y	Y	Y	Y	5
	Hawkey, 2004 ^{207,287} Novartis 0126	Y	Y	Y	Y	Y	5
	Fleischmann, 2003 ^{208,209} Novartis Study 0109	Y	Y	Y	Y	Y	5
	Tannenbaum, 2004 ²¹⁰ Novartis Study 0112	Y	CT	Y	Y	Y	5
	Novartis Study 0128 ²⁸⁰	Y	Y	Y	Y	Y	5
	Novartis Study 2307 ²⁸⁸	Y	Y	Y	Y	Y	5
	Kivitz, 2004 ²¹⁴ Novartis Study 0110	CT	CT	Y	Y	Y	4
	Novartis Study ²²² 0114	Y	Y	Y	Y	Y	5

CT, cannot tell; N, no; Y, yes.

Appendix 8

Details of included economic evaluations

Study: Zabinski RA, *et al.* An economic model for determining costs and consequences of using various treatment alternatives for the management of Arthritis in Canada. *Pharmacoeconomics* 2001;19(Suppl 1):49–58.

Study design	
The research question, including description of alternatives being compared	For patients with OA or RA, comparison of celecoxib and various NSAID/GI protective regimes, in Canada
The viewpoint(s) of the analysis	Ministry of Health
The form of economic evaluation used	Cost–consequence
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	Pooled analysis of 8 Phase III trials
The primary outcome measure(s) for the economic evaluation	GI events, ulcers and deaths
Methods to value health states and other benefits, and subjects (if relevant)	NA
Methods for the estimation of quantities and unit costs	Expert opinion for resource use. Standard health sector sources for unit costs
Currency and price data	Can\$, 1998
Details of any model used	Decision tree model (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	6 months
The discount rate(s)	NA
Details of statistical tests	None
Base-case analysis results	Expected cost for celecoxib slightly higher than for NSAID alone strategy but lower than all others; and celecoxib has the best profile for all outcome measures (e.g. serious GI events, deaths)
Details of sensitivity analysis	One way sensitivity analyses – results most sensitive to probability of UGI distress
The answer to the study question?	“The use of celecoxib could result in the avoidance of a significant number of NSAID-attributable GI adverse events, and ... would not impose an excessive incremental impact on the overall provincial healthcare budget”
Other issues	
Funding source	Pfizer and Pharmacia
MI effects included?	No
NA, not applicable.	

Study: Svarvar P, Aly A. Use of the ACCES model to predict the health economic impact of celecoxib in patients with osteoarthritis or rheumatoid arthritis in Norway. *Rheumatology* 2000;**39**(Suppl 2):43–50.

Study design	
The research question, including description of alternatives being compared	For patients either with RA or OA, comparison of celecoxib, NSAID monotherapy and average NSAID use in Norway
The viewpoint(s) of the analysis	Health sector
The form of economic evaluation used	Cost-effectiveness analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	[As in main publication on ACCES model]
The primary outcome measure(s) for the economic evaluation	GI events avoided Life-years gained
Methods to value health states and other benefits, and subjects (if relevant)	NA
Methods for the estimation of quantities and unit costs	Expert opinion
Currency and price data	Norwegian krone, 1999
Details of any model used	Decision tree – ACCES model
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	NA
Details of statistical tests	None
Base-case analysis results	Celecoxib is dominant over all alternatives, i.e. lower costs and more effective
Details of sensitivity analysis	Base-case result holds for virtually all alternative scenarios considered
The answer to the study question?	“The introduction of celecoxib into the Norwegian NSAID market ... will provide societal benefits at reduced costs”
Other issues	
Funding source	Pfizer
MI effects included?	No

Study: Haglund U, Svarvar P. The Swedish ACCES model: predicting the health economic impact of celecoxib in patients with osteoarthritis or rheumatoid arthritis. *Rheumatology* 2000;**39**(Suppl 2):51–6.

Study design	
The research question, including description of alternatives being compared	For patients either with RA or OA, comparison of celecoxib and NSAID monotherapy
The viewpoint(s) of the analysis	Health sector
The form of economic evaluation used	Cost-effectiveness analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	[As in main publication on ACCES model]
The primary outcome measure(s) for the economic evaluation	GI events avoided Life-years gained
Methods to value health states and other benefits, and subjects (if relevant)	NA
Methods for the estimation of quantities and unit costs	Expert opinion
Currency and price data	Swedish krona, 1999
Details of any model used	Decision tree – ACCES model
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	NA
Details of statistical tests	None
Base case analysis results	Celecoxib is dominant over all alternatives, i.e. lower costs and more effective
Details of sensitivity analysis	Base-case result holds for virtually all alternative scenarios considered
The answer to the study question?	“The use of celecoxib in the Sweden ... will provide societal benefits ... at reduced costs”
Other issues	
Funding source	Pfizer
MI effects included?	No

Study: Moore RA, *et al.* Health economic comparisons of rofecoxib versus conventional nonsteroidal anti-inflammatory drugs for osteoarthritis in the United Kingdom. *J Drug Assess* 2001;4:21–37

Study design	
The research question, including description of alternatives being compared	For patients with OA, comparison of rofecoxib and conventional NSAID
The viewpoint(s) of the analysis	Health sectors only
The form of economic evaluation used	Cost-effectiveness analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	Rofecoxib phase IIb–III clinical trials. Uses data from 8 trials
The primary outcome measure(s) for the economic evaluation	Life-years saved PUB avoided
Methods to value health states and other benefits, and subjects (if relevant)	NA
Methods for the estimation of quantities and unit costs	Expert opinion plus literature sources
Currency and price data	UK£, 1996
Details of any model used	Decision tree (diagram shown)
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	NA
Details of statistical tests	None
Base-case analysis results	Cost/PUB avoided: £10,700 Cost/life-year saved: £15,600
Details of sensitivity analysis	Extensive one-way sensitivity analyses undertaken. Results were most sensitive to the rate of prophylactic gastroprotective agent use
The answer to the study question?	“The importance of rofecoxib represents an important therapeutic advance ... at only a modest additional cost”
Other issues	
Funding source	Merck
MI effects included?	No

Study: Fendrick AM, *et al.* Role of initial NSAID choice and patient risk factors in the prevention of NSAID gastropathy: a decision analysis. *Arthritis Rheum* 2002;47:36–43.

Study design	
The research question, including description of alternatives being compared	Comparison of 2 strategies for long-term NSAID users: 1. generic NSAID used initially and safer NSAIDs reserved for patients experiencing GI adverse events or intolerance 2. safer NSAIDs first line for all patients
The viewpoint(s) of the analysis	Third-party payer
The form of economic evaluation used	Cost-effectiveness analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	MUCOSA trial and COX-2 trials
The primary outcome measure(s) for the economic evaluation	Complicated ulcer prevented
Methods to value health states and other benefits, and subjects (if relevant)	NA
Methods for the estimation of quantities and unit costs	Mainly pricing and charging data
Currency and price data	US\$. Price year not stated
Details of any model used	Markov model (diagram included)
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	NA
Details of statistical tests	None
Base-case analysis results	Strategy 2 (compared with strategy 1) was associated with ICERs of: • \$31,900 per symptomatic ulcer avoided • \$56,700 per complicated ulcer avoided
Details of sensitivity analysis	One-way sensitivity analyses undertaken. Results most sensitive to relative level of GI protection provided by the safer NSAIDs and the ulcer risk of the patient population
The answer to the study question?	“Unrestricted use of NSAIDs ... has the potential to produce important clinical benefits at incremental cost”
Other issues	
Funding source	Unrestricted educational grant from SKB
MI effects included?	No

Study: Tavakoli M. Modelling therapeutic strategies in the treatment of osteoarthritis. *Pharmacoeconomics* 2003;21:443–54.

Study design	
The research question, including description of alternatives being compared	Comparison of 4 weeks treatment for OA with <ul style="list-style-type: none"> • meloxicam • diclofenac • piroxicam
The viewpoint(s) of the analysis	Health sector only
The form of economic evaluation used	Cost-minimisation analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	2 large RCTs, MELISSA and SELECT – pooled estimate used
The primary outcome measure(s) for the economic evaluation	None
Methods to value health states and other benefits, and subjects (if relevant)	NA
Methods for the estimation of quantities and unit costs	Published and routine data sources
Currency and price data	UK£, 1998 (except drug costs, which are at 2000 prices)
Details of any model used	Decision tree model (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	4 weeks
The discount rate(s)	NA
Details of statistical tests	Monte Carlo simulation
Base-case analysis results	Cost per patient: <ul style="list-style-type: none"> • meloxicam £30 • piroxicam £35 • MR diclofenac £51
Details of sensitivity analysis	One-way and probabilistic sensitivity analyses The results suggest “that this drug is the lowest cost option in the treatment of osteoarthritis”
The answer to the study question?	“Meloxicam is a cost-saving drug”
Other issues	
Funding source	None: “The author did not receive any funding for conducting this study”
MI effects included?	Yes

Study: El-Serag HB, *et al.* Prevention of complicated ulcer disease among chronic users of nonsteroidal anti-inflammatory drugs. *Arch Intern Med* 2002;**162**:2105–10.

Study design	
The research question, including description of alternatives being compared	For OA patients, 8 strategies compared: (1) ibuprofen, (2) ibuprofen + PPI, (3) ibuprofen + misoprostol, (4) celecoxib and (5)–(8) comprising <i>H. pylori</i> treatment followed by each of the previous four strategies
The viewpoint(s) of the analysis	Third-party payer
The form of economic evaluation used	Cost-effectiveness analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	Published estimates Very little detail given on synthesis of data Expert opinion in some cases
The primary outcome measure(s) for the economic evaluation	Reduction in UGI events
Methods to value health states and other benefits, and subjects (if relevant)	NA
Methods for the estimation of quantities and unit costs	Data on quantities not stated. Published sources for costs
Currency and price data	US\$, 1999
Details of any model used	Decision tree model (no diagram)
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	NA
Details of statistical tests	None
Base-case analysis results	Most cost-effective strategies were celecoxib and co-therapy with PPIs. But high ICERs (i.e. >\$35,000 per UGI event avoided) for celecoxib in patients with low risk of UGI events. Where risk is high, celecoxib is the dominant strategy
Details of sensitivity analysis	One way and multi-way sensitivity analyses Results most sensitive to baseline risk of UGI event and cost of drugs
The answer to the study question?	COX-2s cost-effective only in patients with high baseline risk of UGI events
Other issues	
Funding source	US Veterans Affairs
MI effects included?	No

Study: Spiegel BM, *et al.* The cost-effectiveness of cyclooxygenase-2 selective inhibitors in the management of chronic arthritis. *Ann Intern Med* 2003;**138**:795–806.

Study design				
The research question, including description of alternatives being compared		Patients with RA or OA with moderate or severe arthritic pain and without GI symptoms. Comparison of:		
		<ul style="list-style-type: none"> • COX-2 (either celecoxib or rofecoxib) • Non-selective NSAID (naproxen) 		
		Note: patients with history of ulcer complications considered as part of sensitivity analysis		
The viewpoint(s) of the analysis		Third-party payer		
The form of economic evaluation used		Cost–utility analysis		
Data collection				
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)		Systematic review and meta-analysis of trials. Pooled estimate for COX-2s (i.e. both celecoxib and rofecoxib) derived		
The primary outcome measure(s) for the economic evaluation		QALYs		
Methods to value health states and other benefits, and subjects (if relevant)		Valuation method not stated Utility estimates taken from a single published source (Groeneveld <i>et al.</i> , 2001 ⁴⁶²)		
Methods for the estimation of quantities and unit costs		Taken from routine health sector sources, including fee schedules and price lists		
Currency and price data		US\$ 2002		
Details of any model used		Decision tree model (diagram provided)		
Analysis and interpretation of results				
Time horizon of costs and benefits		Lifetime		
The discount rate(s)		3% for both costs and effects		
Details of statistical tests		Monte Carlo simulation for probabilistic sensitivity analysis		
Base-case analysis results		See data below		
Details of sensitivity analysis		One-way and probabilistic sensitivity analyses (assuming triangular distributions for all parameters) High-risk cohort modelled Inclusion of CV events “The coxib strategy became dominant when the cost of the coxibs was reduced by 90% of the current average wholesale price”		
The answer to the study question?		In the management of average-risk patients, coxibs are not cost-effective, but may provide an acceptable ICER in the subgroup of patients with a history of bleeding ulcers		
Other issues				
Funding source		US National Institute of Health and VA		
MI effects included?		Yes, as part of sensitivity analyses		
Study results				
		Cost (US\$)	QALYs	ICER (US\$)
Base case	Naproxen	4,859	15.2613	
	Coxib	16,443	15.3033	275,800
Including CV events	Naproxen	2,037	15.2539	
	Coxib	16,620	15.2832	395,000
High-risk cohort (previous ulcer haemorrhage)	Naproxen	14,294	14.7235	
	Coxib	19,015	14.8081	55,800

Study: Rafter N, *et al.* Listing rofecoxib and celecoxib in the Pharmaceutical Schedule. *PHARMAC Report* 2003.

Study design	
The research question, including description of alternatives being compared	Comparison of COX-2s (celecoxib and rofecoxib) and NSAIDs (i.e. ibuprofen, diclofenac) Looked separately at average risk population and high-risk population (defined as those with previous UGI event) of patients with RA or OA
The viewpoint(s) of the analysis	Healthcare sector
The form of economic evaluation used	Cost-utility analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	CLASS trial – celecoxib VIGOR trial – rofecoxib Plus other FDA sources
The primary outcome measure(s) for the economic evaluation	QALYs
Methods to value health states and other benefits, and subjects (if relevant)	Utility weights taken from range of published sources, including CCOHTA report
Methods for the estimation of quantities and unit costs	Routine health sector sources (e.g. N2 DRG costs) plus other published estimates
Currency and price data	NZ\$, 2003
Details of any model used	Amended version of Maetzel model – Markov (diagram shown)
Analysis and interpretation of results	
Time horizon of costs and benefits	5 years
The discount rate(s)	10% in base case (but not varied in sensitivity analyses?)
Details of statistical tests	None
Base-case analysis results	Naproxen dominates rofecoxib Diclofenac dominates celecoxib Celecoxib vs ibuprofen: <ul style="list-style-type: none"> • ICER for average risk population: \$482,000/QALY gained • ICER for high-risk population: \$88,000/QALY gained
Details of sensitivity analysis	One-way, two-way and multi-way sensitivity analyses performed Only in extreme scenarios did celecoxib (vs ibuprofen) tend towards being cost-effective
The answer to the study question?	“Neither celecoxib nor rofecoxib provides sufficient incremental health benefits per dollar compared to NSAIDs to justify listing it on the New Zealand Pharmaceutical Schedule”
Other issues	
Funding source	Accident Compensation Corporation and Australasian Faculty of Public Health Medicine
MI effects included	Yes

Study: Maetzel A, *et al.* The cost effectiveness of rofecoxib and celecoxib in patients with osteoarthritis or rheumatoid arthritis. *Arthritis Rheum* 2003;**49**:283–92.

Study design	
The research question, including description of alternatives being compared	In average-risk patients with RA or OA comparison of: <ul style="list-style-type: none"> • celecoxib vs diclofenac vs ibuprofen • rofecoxib vs naproxen In high-risk patients with RA or OA comparison of: <ul style="list-style-type: none"> • rofecoxib vs naproxen + PPI vs rofecoxib + PPI • celecoxib vs ibuprofen + PPI vs diclofenac + PPI vs celecoxib + PPI Note: 'high-risk' defined as all patients who have a positive history of a clinical UGI event
The viewpoint(s) of the analysis	Health sector perspective
The form of economic evaluation used	Cost-effectiveness analysis and cost-utility analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	CLASS trial – celecoxib VIGOR trial – rofecoxib Plus FDA sources
The primary outcome measure(s) for the economic evaluation	Clinical UGI event Complicated UGI event Life-years QALYs
Methods to value health states and other benefits, and subjects (if relevant)	Study-specific standard gamble utilities generated using 60 members of the general public
Methods for the estimation of quantities and unit costs	Routine health sector and other published sources plus physician's focus groups
Currency and price data	Can\$, 1999
Details of any model used	Markov model, developed by authors (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	5 years
The discount rate(s)	5% for both costs and QALYs
Details of statistical tests	None
Base-case analysis results	See data below
Details of sensitivity analysis	Extensive one-way analysis on cost and QALY parameters. "Rofecoxib would be cost saving at a price of approximately \$0.33 per dose ... and celecoxib would be cost saving ... at a price of approximately \$0.25 per 100 mg twice per day"
The answer to the study question?	Prescribing of celecoxib and rofecoxib is only cost-effective in high-risk patients.
Other issues	
Funding source	Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
MI effects included?	Yes

continued

Study results					
		Costs (Can\$)	Complicated UGI events	QALYs	ICER (cost/QALY gained) (Can\$)
Average-risk patients	Naproxen	1,576	7.70	2.8938	
	Rofecoxib	3,173	3.39	2.8997	271,000
	Ibuprofen	1,141	6.36	2.8990	
	Diclofenac	2,570	2.68	2.9104	125,000
	Celecoxib	3,371	2.48	2.9095	Dominated by diclofenac
High-risk patients	Rofecoxib	4,090	7.45	2.8851	
	Naproxen + PPI	4,766	11.31	2.8816	Dominated by rofecoxib
	Rofecoxib + PPI	6,486	5.13	2.8936	281,000
	Celecoxib	4,327	5.54	2.9003	
	Ibuprofen + PPI	4,414	9.49	2.8894	Dominated by celecoxib
	Diclofenac + PPI	5,980	4.11	2.9064	271,000
	Celecoxib + PPI	6,746	3.81	2.9057	Dominated by diclofenac + PPI

Study: Kamath CC, *et al.* The cost-effectiveness of acetaminophen, NSAIDs, and selective COX-2 inhibitors in the treatment of symptomatic knee osteoarthritis. *Value Health* 2003;6:144–57.

Study design			
The research question, including description of alternatives being compared	For patients with symptomatic knee OA, comparison of: <ul style="list-style-type: none"> • rofecoxib • celecoxib • high-dose acetaminophen • ibuprofen (with or without misoprostol) 		
The viewpoint(s) of the analysis	Direct medical costs only		
The form of economic evaluation used	Cost-effectiveness analysis		
Data collection			
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	For adverse GI events: <ul style="list-style-type: none"> • rofecoxib – Langman <i>et al.</i> (1999³²) • celecoxib – CLASS and other relevant trials For pain: FDA reviews and assumptions		
The primary outcome measure(s) for the economic evaluation	Adverse events averted Achievement of minimally perceptible clinical improvement (MPCI)		
Methods to value health states and other benefits, and subjects (if relevant)	NA		
Methods for the estimation of quantities and unit costs	Resource use and costs from billing data (US) and assumptions		
Currency and price data	US\$, 2000 prices		
Details of any model used	Decision tree model (diagram shown) (based on Maetzel model)		
Analysis and interpretation of results			
Time horizon of costs and benefits	6 months		
The discount rate(s)	NA		
Details of statistical tests	Monte Carlo simulation undertaken for probability sensitivity analysis		
Base-case analysis results	See data below		
Details of sensitivity analysis	One-way, two-way and probabilistic sensitivity analyses performed “When effectiveness was defined as the number of GI events averted, acetaminophen had the highest average net benefit in 100% of the Monte Carlo simulations”		
The answer to the study question?	Acetaminophen dominates in terms of cost per GI event avoided. In terms of pain relief, only if one values pain relief above \$14,150 is rofecoxib likely to be optimal		
Other issues			
Funding source	McNeil Consumer Healthcare (in part)		
MI effects included?	No		
Study results			
	Cost (US\$)	Adverse events averted	Patients achieving MPCI response
Acetaminophen	63,000	994.9	750
Ibuprofen	112,000	979.5	830
Rofecoxib	471,000	990.8	860
Celecoxib	474,000	990.3	790
Ibuprofen + misoprostol	556,000	987.7	830

Study: Bae SC, *et al.* Cost-effectiveness of low dose corticosteroids versus non-steroidal anti-inflammatory drugs and COX-2 specific inhibitors in the long-term treatment of rheumatoid arthritis. *Rheumatology* 2003;42:46–53.

Study design			
The research question, including description of alternatives being compared		Main analysis: compared corticosteroids and NSAIDs Supplementary analysis: compared COX-2 and corticosteroids COX-2s considered: celecoxib and rofecoxib (not analysed separately) Patients with RA	
The viewpoint(s) of the analysis		Authors state that societal perspective considered but appears to be health sector only	
The form of economic evaluation used		Cost–utility analysis	
Data collection			
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)		Strategies assumed to be equally effective. GI complications rate for COX-2 taken from published meta analysis (Goldstein <i>et al.</i> , 1999 ⁴⁶³)	
The primary outcome measure(s) for the economic evaluation		QALYs	
Methods to value health states and other benefits, and subjects (if relevant)		Time trade-off and standard gamble – quality of life adjustments taken from a variety of sources	
Methods for the estimation of quantities and unit costs		Incidence of adverse events from meta-analysis Cost of treatment of adverse events from a variety of sources	
Currency and price data		US\$, 1999	
Details of any model used		Markov model – very few details given (no diagram)	
Analysis and interpretation of results			
Time horizon of costs and benefits		Lifetime – for base case Patients 50 years old at start of model	
The discount rate(s)		3% for ‘all values’	
Details of statistical tests		None employed	
Base-case analysis results		See data below	
Details of sensitivity analysis		For COX-2, only varied cost “COX-2 inhibitors were superior to corticosteroids when the cost was less than \$707”	
The answer to the study question?		“Corticosteroids are more cost-effective than NSAIDs and COX-2 inhibitors in the long-term treatment of RA”	
Other issues			
Funding source		Korean Ministry of Health and Welfare and Arthritis Foundation	
MI effects included?		No	
Study results			
	Cost (US\$)	QALYs	ICERs (US\$)
Corticosteroids	43,800	11.67	COX-2 vs NSAID: 51,700
NSAIDs	44,900	11.46	COX-2 vs corticosteroid: 137,000
COX-2	63,000	11.81	

Study: Marshall JK, *et al.* Incremental cost-effectiveness analysis comparing rofecoxib with nonselective NSAIDs in osteoarthritis. *Pharmacoeconomics* 2001;**19**:1039–49.

Study design	
The research question, including description of alternatives being compared	For patients with OA in whom paracetamol has failed, comparison of rofecoxib and non-selective NSAIDs
The viewpoint(s) of the analysis	Ontario Ministry of Health
The form of economic evaluation used	Cost-effectiveness analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	GI event rates taken from pooled analysis of eight Phase IIb/III clinical trials
The primary outcome measure(s) for the economic evaluation	PUB avoided
Methods to value health states and other benefits, and subjects (if relevant)	Published and routine health sector sources
Methods for the estimation of quantities and unit costs	NA
Currency and price data	Can\$, 1999
Details of any model used	Decision tree model (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	NA
Details of statistical tests	None
Base-case analysis results	ICER: \$2246 per PUB averted
Details of sensitivity analysis	Wide range of one-way sensitivity analyses performed. Most sensitivity analysis scenarios still favour rofecoxib.
The answer to the study question?	“Rofecoxib may represent a cost-effective alternative to non-selective NSAIDs”
Other issues	
Funding source	Merck
MI effects included?	No

Study: Pellissier JM, *et al.* Economic evaluation of rofecoxib versus nonselective nonsteroidal anti-inflammatory drugs for the treatment of osteoarthritis. *Clin Ther* 2001;**23**:1061–79.

Study design	
The research question, including description of alternatives being compared	For OA patients, comparison of rofecoxib and non-selective NSAIDs
The viewpoint(s) of the analysis	Health sector
The form of economic evaluation used	Cost-effectiveness analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	GI event data taken from pooled analysis of rofecoxib trials
The primary outcome measure(s) for the economic evaluation	PUBs avoided Life-years gained
Methods to value health states and other benefits, and subjects (if relevant)	NA
Methods for the estimation of quantities and unit costs	Data taken from routine sources, e.g. fee schedules, diagnosis related groups costs
Currency and price data	US\$, 1998
Details of any model used	Decision tree model (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	1 year
The discount rate(s)	NA
Details of statistical tests	None
Base-case analysis results	Base case: • cost per PUB avoided: \$4700 • cost per life-year saved: \$18,600 Adjustment for 'silent ulcers': rofecoxib is cost saving
Details of sensitivity analysis	Wide ranging one-way sensitivity analysis Almost all scenarios explored gave a more favourable result for rofecoxib
The answer to the study question?	"Costs per life-year saved with rofecoxib versus NSAIDs were well within accepted benchmarks for cost-effectiveness"
Other issues	
Funding source	Merck
MI effects included?	No

Study: Chancellor JVM. Economic evaluation of celecoxib, a new cyclo-oxygenase 2 specific inhibitor, in Switzerland. *Pharmacoeconomics* 2001;**19**(Suppl 1):59–75.

Study design	
The research question, including description of alternatives being compared	For arthritis patients, comparison of: <ul style="list-style-type: none"> • celecoxib • NSAID alone • NSAID plus PPI • NSAID plus H2RA • NSAID plus misoprostol • diclofenac/misoprostol
The viewpoint(s) of the analysis	Healthcare sector
The form of economic evaluation used	Cost–consequence analysis
Data collection	
The source(s) of effectiveness estimates used and method of synthesis or meta-analysis (if based on an overview of a number of effectiveness studies)	GI event rates derived from pooled estimates from clinical trials
The primary outcome measure(s) for the economic evaluation	GI events averted
Methods to value health states and other benefits, and subjects (if relevant)	NA
Methods for the estimation of quantities and unit costs	Expert opinion for resource estimates Routine sources for unit costs
Currency and price data	Swiss franc
Details of any model used	Decision tree model – celecoxib outcomes measurement evaluation tool (COMET) (diagram provided)
Analysis and interpretation of results	
Time horizon of costs and benefits	6 months
The discount rate(s)	NA
Details of statistical tests	Monte Carlo simulation
Base-case analysis results	Celecoxib associated with lowest cost and the fewest number of GI events, i.e. dominant therapy
Details of sensitivity analysis	Probabilistic sensitivity analysis performed, which confirmed dominance of celecoxib
The answer to the study question?	“Celecoxib is predicted to be the most cost-effective of the treatments considered for managing arthritis patients in Switzerland”
Other issues	
Funding source	Pharmacia
MI effects included?	No

Appendix 9

Calculation of probabilities for initial cycle

Table 114 was obtained by combining cells in Table 4 in Langman *et al.*⁷⁶

Consider the case where ibuprofen alone is the first line of treatment, the most likely course of action in primary care. Figure 52 shows four possible outcomes in Table 114. We have assumed that where patients are subsequently given an NSAID with a gastroprotective agent (GPA) a PPI is added: 'Add PPI' in our model. We have also assumed that where patients are subsequently given a different NSAID this equates to 'Switch to

N2' in our model. The probabilities of reaching the various branches are as shown in the figure.

Then we have:

$$p_{RemainN1} = 0.026 + 0.514 = 0.540$$

$$p_{AddPPItoN1} = 0.026/0.540 = 0.048$$

$$p_{DropN1} = 0.315/(1 - 0.540) = 0.685$$

(In the model, the probabilities for the outcomes are supplied as parameters and the probabilities in the tree are calculated by equations corresponding to the calculations shown above.)

TABLE 114 First and second prescriptions with and without GPAs among new patients

First prescription	Second prescription				Total
	No drug (%)	Same drug alone (%)	Different NSAID alone (%)	NSAID plus GPA (%)	
Ibuprofen alone	1059 (31.5)	1726 (51.4)	486 (14.5)	86 (2.6)	3357
Diclofenac alone	591 (26.5)	1342 (60.3)	213 (9.6)	80 (3.6)	2226

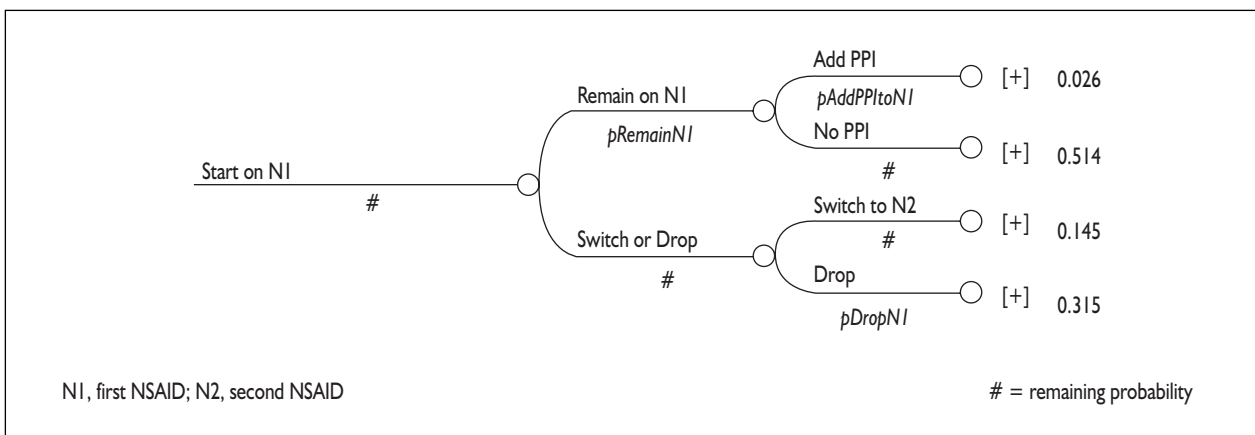


FIGURE 52 Changes from initial prescription

Appendix 10

Calculation of probabilities for main Markov cycles

The data for the model include risks of any GI event, clinical GI event and complicated GI event. For ibuprofen and diclofenac, these are given as absolute risks. For COX-2 inhibitors, RRs are given, compared with ibuprofen. RRs are also included for use of PPI and for previous GI event.

These are then combined to give the probability of any GI event, probability of clinical GI event conditional on any GI event and probability of complicated GI event conditional on clinical GI event. For example, consider a patient on ibuprofen with PPI, post-GI but not post-MI. The relevant risks are as follows:

Baseline risks for 'average' patient	Risk (per year)
Risk of any GI event on ibuprofen	0.3115
Risk of clinical GI event	0.032
Risk of complicated GI event	0.0114
RRs to be applied:	
PPI use (applies to all GI events)	0.4
Prior GI (applies to clinical and complicated GI events only)	2.6

These then convert to the following risks and probabilities (results shown rounded, but full accuracy maintained during calculations):

Event	Risk (per year)	Probability of event occurring in 3-month cycle	Probability (conditional on previous event)
Any GI event	0.1246	0.0307	
Clinical GI event	0.0333	0.0083	0.2702
Complicated GI event	0.0119	0.0030	0.3572

Full calculations for clinical GI events (others are similar):

$$\text{risk per year: } 0.032 \times 0.4 \times 2.6 = 0.0333$$

$$\text{probability in cycle: } 1 - \exp(-0.333 \times 0.25) = 0.0083$$

$$\text{probability conditional on any GI event: } 0.0083/0.0307 = 0.2702.$$

The following probabilities are taken to be the same for all drugs:

Hospitalisation given complicated GI event	0.432
Surgery given hospitalisation	0.085
Death given complicated GI event	0.03

Appendix 11

Univariate sensitivity analysis results

Varying the relative risk of adding a PPI – ibuprofen as the comparator Single COX-2 selective NSAIDs against ibuprofen (RR adding PPI: 0.6)

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALYs)
Ibuprofen	526.83		3.18624		
Celecoxib (LD)	1,458.77	931.94	3.19668	0.01044	89,300
Celecoxib (HD)	2,567.52	2,040.69	3.19668	0.01044	195,000
Etodolac (branded)	1,145.68	618.85	3.19768	0.01144	54,100
Etodolac (generic)	789.57	262.74	3.19768	0.01144	23,000
Etoricoxib	1,527.33	1,000.50	3.21735	0.03111	32,200
Lumiracoxib	1,230.66	703.83	3.19265	0.00641	110,000
Meloxicam (LD)	809.24	282.41	3.21090	0.02466	11,500
Meloxicam (HD)	1,009.77	482.94	3.21090	0.02466	19,600
Rofecoxib	1,562.90	1,036.07	3.19380	0.00756	137,000
Valdecoxib	1,487.80	960.97	3.21082	0.02458	39,100

HD, high-dose; LD, low-dose.

Single COX-2 selective NSAIDs against ibuprofen plus PPI (RR adding PPI: 0.6)

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER ^a (£ per QALYs)
Ibuprofen + PPI	968.14		3.20526		
Celecoxib (LD)	1,458.77	490.63	3.19668	-0.00858	D
Celecoxib (HD)	2,567.52	1,599.38	3.19668	-0.00858	D
Etodolac (branded)	1,145.68	177.54	3.19768	-0.00758	D
Etodolac (generic)	789.57	-178.57	3.19768	-0.00758	23,600
Etoricoxib	1,527.33	559.19	3.21735	0.01209	46,300
Lumiracoxib	1,230.66	262.52	3.19265	-0.01261	D
Meloxicam (LD)	809.24	-158.90	3.21090	0.00564	^b
Meloxicam (HD)	1,009.77	41.63	3.21090	0.00564	7,380
Rofecoxib	1,562.90	594.76	3.19380	-0.01146	D
Valdecoxib	1,487.80	519.66	3.21082	0.00556	93,500

^a ICER in *italics* means that both incremental values are negative; D means that COX-2 selective NSAID is dominated by ibuprofen plus PPI.
^b Meloxicam (LD) dominates ibuprofen plus PPI.

Single COX-2 selective NSAIDs against ibuprofen plus PPI for patients with previous history of GI events (RR adding PPI: 0.6)

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER ^a (£ per QALYs)
Ibuprofen + PPI	1,011.85		3.19599		
Celecoxib (LD)	1,461.30	449.45	3.18933	-0.00666	D
Celecoxib (HD)	2,544.53	1,532.68	3.18933	-0.00666	D
Etodolac (branded)	1,144.42	132.57	3.19255	-0.00344	D
Etodolac (generic)	795.13	-216.72	3.19255	-0.00344	63,000
Etoricoxib	1,509.37	497.52	3.21175	0.01576	31,600
Lumiracoxib	1,237.48	225.63	3.18706	-0.00893	D
Meloxicam (LD)	834.98	-176.87	3.20291	0.00692	^b
Meloxicam (HD)	1,031.26	19.41	3.20291	0.00692	2,800
Rofecoxib	1,549.58	537.73	3.18798	-0.00801	D
Valdecoxib	1,485.29	473.44	3.20592	0.00993	47,700

^a ICER in *italics* means that both incremental values are negative. D means that COX-2 selective NSAID is dominated by ibuprofen plus PPI.

^b Meloxicam (LD) dominates ibuprofen plus PPI.

Varying the relative risk of GI events and MI – ibuprofen as the comparator

Single COX-2 selective NSAIDs against ibuprofen – results with RR for all types of GI event at the lower CIs (favouring COX-2 selective NSAIDs)

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALYs)
Ibuprofen	518.43		3.19183		
Celecoxib (LD)	1,451.06	932.63	3.20499	0.01316	70,900
Celecoxib (HD)	2,565.24	2,046.81	3.20499	0.01316	156,000
Etodolac (branded)	1,134.91	616.48	3.21070	0.01887	32,700
Etodolac (generic)	776.53	258.10	3.21070	0.01887	13,700
Etoricoxib	1,434.31	915.88	3.23421	0.04238	21,600
Lumiracoxib	1,222.85	704.42	3.20035	0.00852	82,700
Meloxicam (LD)	773.75	255.32	3.22006	0.02823	9,040
Meloxicam (HD)	975.69	457.26	3.22006	0.02823	16,200
Rofecoxib	1,474.12	955.69	3.21732	0.02549	37,500
Valdecoxib	1,460.35	941.92	3.22090	0.02907	32,400

Single COX-2 selective NSAIDs against ibuprofen – results with RR for all types of GI event at the upper CIs (favouring non-selective NSAIDs)

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER ^a (£ per QALYs)
Ibuprofen	521.75		3.19107		
Celecoxib (LD)	1,460.01	938.26	3.19598	0.00491	191,000
Celecoxib (HD)	2,561.98	2,040.23	3.19598	0.00491	416,000
Etodolac (branded)	1,154.47	632.72	3.18770	-0.00337	D
Etodolac (generic)	804.80	283.05	3.18770	-0.00337	D
Etoricoxib	1,586.25	1,064.50	3.18021	-0.01086	D
Lumiracoxib	1,231.61	709.86	3.19375	0.00268	265,000
Meloxicam (LD)	833.98	312.23	3.20503	0.01396	22,400
Meloxicam (HD)	1,032.06	510.31	3.20503	0.01396	36,600
Rofecoxib	1,580.67	1,058.92	3.15949	-0.03158	D
Valdecoxib	1,524.50	1,002.75	3.20073	0.00966	104,000

^a D means that COX-2 selective NSAID is dominated by ibuprofen.

Single COX-2 selective NSAIDs against ibuprofen – results with RR for MI at the lower CIs (favouring COX-2 selective NSAIDs)

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALYs)
Ibuprofen	520.06		3.19150		
Celecoxib (LD)	1,437.38	917.32	3.20360	0.0121	75,800
Celecoxib (HD)	2,547.11	2,027.05	3.20360	0.0121	168,000
Etodolac (branded)	1,124.73	604.67	3.20454	0.01304	46,400
Etodolac (generic)	768.37	248.31	3.20454	0.01304	19,000
Etoricoxib	1,490.59	970.53	3.22447	0.03297	29,400
Lumiracoxib	1,206.97	686.91	3.20027	0.00877	78,300
Meloxicam (LD)	798.23	278.17	3.21535	0.02385	11,700
Meloxicam (HD)	998.93	478.87	3.21535	0.02385	20,100
Rofecoxib	1,523.64	1,003.58	3.20335	0.01185	84,700
Valdecoxib	1,481.14	961.08	3.21504	0.02354	40,800

Single COX-2 selective NSAIDs against ibuprofen – results with RR for MI at the upper CIs (favouring non-selective NSAIDs)

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER ^a (£ per QALYs)
Ibuprofen	520.06		3.19150		
Celecoxib (LD)	1,485.64	965.58	3.19649	0.00499	194,000
Celecoxib (HD)	2,594.77	2,074.71	3.19649	0.00499	416,000
Etodolac (branded)	1,173.26	653.20	3.19742	0.00592	110,000
Etodolac (generic)	817.09	297.03	3.19742	0.00592	50,200
Etoricoxib	2,250.25	1,730.19	3.11143	-0.08007	D
Lumiracoxib	1,265.26	745.20	3.19171	0.00021	3,550,000
Meloxicam (LD)	982.53	462.47	3.18834	-0.00316	D
Meloxicam (HD)	1,182.82	662.76	3.18834	-0.00316	D
Rofecoxib	1,634.61	1,114.55	3.18697	-0.00453	D
Valdecoxib	1,503.00	982.94	3.21182	0.02032	48,400

^a D means that COX-2 selective NSAID is dominated by ibuprofen.

Single COX-2 selective NSAIDs against ibuprofen – results with RR for MI = 1.0

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALYs)
Ibuprofen	520.06		3.19150		
Celecoxib (LD)	1,437.12	917.06	3.20363	0.01213	75,600
Celecoxib (HD)	2,546.86	2,026.80	3.20363	0.01213	167,000
Etodolac (branded)	1,124.47	604.41	3.20458	0.01308	46,200
Etodolac (generic)	768.11	248.05	3.20458	0.01308	19,000
Etoricoxib	1,512.54	992.48	3.22123	0.02973	33,400
Lumiracoxib	1,210.12	690.06	3.19981	0.00831	83,100
Meloxicam (LD)	821.52	301.46	3.21194	0.02044	14,700
Meloxicam (HD)	1,022.17	502.11	3.21194	0.02044	24,600
Rofecoxib	1,515.11	995.05	3.20460	0.01310	76,000
Valdecoxib	1,503.14	983.08	3.21180	0.02030	48,400

Single COX-2 selective NSAIDs against ibuprofen – results with utility for arthritis = 0.82

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (£ per QALYs)
Ibuprofen	520.06		3.77784		
Celecoxib (LD)	1,455.04	934.98	3.79292	0.01508	62,000
Celecoxib (HD)	2,564.55	2,044.49	3.79292	0.01508	136,000
Etodolac (branded)	1,142.49	622.43	3.79361	0.01577	39,500
Etodolac (generic)	786.20	266.14	3.79361	0.01577	16,900
Etoricoxib	1,526.05	1,005.99	3.82303	0.04519	22,300
Lumiracoxib	1,226.73	706.67	3.78593	0.00809	87,400
Meloxicam (LD)	805.73	285.67	3.81322	0.03538	8,070
Meloxicam (HD)	1,006.41	486.35	3.81322	0.03538	13,800
Rofecoxib	1,559.58	1,039.52	3.78933	0.01149	90,500
Valdecoxib	1,485.55	965.49	3.81203	0.03419	28,200

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (<http://www.hta.ac.uk>) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.