Alberta Heritage Foundation
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Celecoxib for the Treatment of Pain in Osteoarthritis and Rheumatoid Arthritis

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25 YEARS OF EXCELLENCE

AHFMR
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- Dr Alan Rostom, Gastrointestinal Clinical Research Unit, University of Ottawa, Ottawa
- Dr Rod Taylor, Department of Public Health and Epidemiology, University of Birmingham, Birmingham, United Kingdom

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CONFLICT OF INTEREST

Conflict of interest is considered to be financial interest, either direct or indirect, that would be affected by the research contained in this report, or creation of a situation where an author's and/or other contributor's judgment could be unduly influenced by a secondary interest such as personal advancement.

Based on the statement above the following persons have potential conflict of interest:

- Dr Martin Atkinson was the chair of a Medical Advisory Board for the Pfizer Canada Inc.
- Dr Joanne Homik has acted as consultant to both Pfizer Canada Inc. and Merck Frosst Canada Ltd.
- Dr Alan Rostom was the recipient of research grants from Novartis and Merck Frosst Canada Ltd.

EXECUTIVE SUMMARY

Background

Arthritis including osteoarthritis (OA) and rheumatoid arthritis (RA) is a leading cause of pain and the most common cause of long-term disability and health care utilization in Canada.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of arthritis but are associated with upper gastrointestinal (GI) adverse events. Cyclo-oxygenase 2 (COX-2) inhibitors including celecoxib, a different class of NSAIDs, were developed on the premise that they would avoid GI complications.

Objectives

To present the current evidence on the efficacy/effectiveness and safety of celecoxib (Celebrex®) for the treatment of pain in patients with OA and RA.

Results

Two SRs (meta-analyses) of RCTs assessed the effectiveness (pain reduction and functional improvement) and safety (endoscopic evaluation, gastric/duodenal erosions or ulcers) of celecoxib administered to patients who have OA and RA.

At three months follow-up, celecoxib at any dose (80 mg to 800 mg) showed a statistically significant (SS) improvement compared with placebo in patients with RA. At 400 mg daily for three months, celecoxib, when compared with naproxen 1000 mg daily, showed a SS improvement only on the basis of patient's and physician's global assessments. At six months, celecoxib 400 mg daily was just as effective as diclofenac 150 mg daily.

As determined by endoscopic evaluation, gastroduodenal erosions or ulcers were significantly reduced in RA and OA patients after taking 400 mg daily of celecoxib compared with diclofenac (150 mg daily) after six months, and naproxen (1000 mg daily) and ibuprofen (2400 mg daily) after three months.

Five RCTs were located that assessed the outcomes of celecoxib administered to patients with OA of the knee and/or hip and patients with RA.

Celecoxib 200 mg daily showed the same efficacy when compared with different active drugs (COX-2 inhibitors, nimesulide 100 mg daily and rofecoxib 25 mg daily; or diclofenac 150 mg daily), was superior to acetaminophen 1,000 mg four times daily, and provided a SS improvement when compared with placebo in patients with OA for periods of follow-up between two weeks and one year.

The safety analysis indicated that celecoxib 800 mg daily was superior in dyspepsia tolerability compared with diclofenac 150 mg daily. Celecoxib 200 mg daily showed a similar safety profile when compared with other active treatments (selective and non-selective NSAIDs). None of the RCTs investigated gastroduodenal erosions or ulcers.

The costs of COX-2 inhibitors such as celecoxib are approximately twice as high as the cost for non-selective NSAIDs.

Conclusions

Overall, short-term use of celecoxib was equivalent to non-selective NSAIDs (naproxen and diclofenac) and other COX-2 inhibitors (nimesulide and rofecoxib) and was superior to acetaminophen in reducing pain and improving function for patients with RA and OA. Short-term use of celecoxib was associated with a reduction in rates of gastroduodenal erosions or ulcers compared with those for non-selective NSAIDs (naproxen, ibuprofen, and diclofenac) in patients with RA and OA.

Many questions remain to be addressed about the long-term safety of celecoxib compared with non-selective NSAIDs and about the combination treatment of NSAIDs and other types of drugs.

Health Canada recommended usage restrictions for Celebrex® beginning in April 2005. Celebrex® should not be used in patients who have had a heart attack or stroke, serious chest pain related to hearth disease, or congestive heart failure. Celebrex® may increase the risk of cardiovascular events in patients with high blood pressure, high cholesterol, diabetes, and smoking. Also, Celebrex® should be prescribed and used at the lowest possible dose and for the shortest, necessary period of time.

Methodology

A systematic search of PubMed, EMBASE, HealthStar, The Cochrane Library, Science Citation Index, and the web sites of various health technology assessment agencies, research registers, and guideline sites from 1998 onwards was performed. The analysis was limited to studies on celecoxib published in the English language beginning with 1998 systematic reviews (SRs) and, since July 2002, randomized controlled studies (RCTs). Position papers and guidance reports, along with the regulatory status of COX-2 inhibitors, are also included.

Reference

Moga C, Harstall C, Tang Z. *Celecoxib for the treatment of pain in osteoarthritis and rheumatoid arthritis.* Edmonton, AB: Alberta Heritage Foundation for Medical Research; 2005 (IP #24)

ABBREVIATIONS

ACR - The American College of Rheumatology
ACR-20 - The American College of Rheumatology responder index
AE - adverse event
APS - American Pain Society
ARR - absolute risk reduction
BC - British Columbia
CER - control event rate
CI – confidence interval
CLASS - Celecoxib Long-term Arthritis Safety Study
COX-1 - cyclo-oxygenase 1
COX-2 - cyclo-oxygenase 2
CPS – Compendium of Pharmaceuticals and Specialties
DMARDs - disease modifier anti-rheumatic drugs
EER - experimental event rate
EULAR - European League Against Rheumatism
FDA - Food and Drug Administration
GI – gastrointestinal
HAQ - Health Assessment Questionnaire index
HC - Health Canada
IASP - International Association for the Study of Pain
LU - limited use
NICE – National Institute for Clinical Excellence (UK)
NNH - number needed to harm
NSAID – non-steroidal anti-inflammatory drug
OA – osteoarthritis
OMERACT - Outcome Measures for Rheumatoid Arthritis Clinical Trials
PGART - patient's global assessment of response to therapy
PGs - prostaglandins

POB - perforations, obstruction, and bleeding

PUB - perforations, ulcers, and bleeding

RA – rheumatoid arthritis

RCT – randomized controlled trial

RR - relative risk

SA - special authority

SODA - Severity of Dyspepsia Assessment questionnaire

SR - systematic review

SS – statistically significant

UGI - upper gastrointestinal

VAS - Visual Analogue Scale

WOMAC - The Western Ontario and McMaster Universities osteoarthritis index

CONTENTS

Tables and Figures

SCOPE

This report (information paper) has been produced in response to a request from the Information Sharing Group on Chronic Pain for evidence on the efficacy/effectiveness and safety of cyclo-oxygenase 2 (COX-2) inhibitors for the treatment of (chronic) pain in patients with rheumatoid arthritis (RA) and osteoarthritis (OA).

Only two systematic reviews (SRs) met the inclusion criteria and are focused on the efficacy/effectiveness of celecoxib for patients with RA and the safety of celecoxib for patients with OA and RA. SRs that presented results from confidential studies in their review and those that included randomized control trials (RCTs) in their analyses with variability in the follow-up periods and/or lumped together drugs based on class (group non-selective non-steroidal anti-inflammatory drugs and COX-2 inhibitors) or different doses were excluded (see Appendixes A and E).

In addition, in order to strengthen the current evidence, another search was done to identify RCTs on celecoxib published since the search date of the SRs. These RCTs are also included in the report. As the SRs did not differentiate between chronic and acute pain in their analyses of the primary studies, all RCTs that assessed the therapeutic and safety outcomes of celecoxib for RA and OA patients, whether it was prescribed for chronic or acute pain, were included.

Position papers and guidance reports, along with the regulatory status of the COX-2 inhibitors, are also presented.

BACKGROUND

Pain is defined as *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"* by the International Association for the Study of Pain (IASP) [1-3]. In general, pain falls into three main categories: acute, chronic, and cancer related. IASP defines chronic pain as pain that has persisted beyond the normal tissue healing time (usually about three months). This report focuses on pain not related to cancer in patients with rheumatoid arthritis (RA) and osteoarthritis (OA).

Measurement of pain includes measures of pain intensity and/or pain relief. Categorical measures are the most common tools used in pain measurement. Verbal numerical scales and global subjective efficacy ratings are also used to measure pain [4,5]. For patients with RA or OA, the American Pain Society (APS) suggested that *"because pain is a major cause of disability, assessment of functional status should be included in pain assessment"* [6].

The American College of Rheumatology (ACR) classification of functional status in the RA responder index (ACR-20), and the Western Ontario and McMaster Universities (WOMAC) OA index are the indexes used most frequently to measure functional status in patients with RA and OA, respectively. The efficacy of the treatment of patients with RA may also be measured by the Outcome Measures for Rheumatoid Arthritis Clinical Trials (OMERACT) outcomes (number of tender and swollen joints per patient, pain, physician and patient global assessment, functional status, acute phase reactants, and radiological damage).

In most patients with (chronic) arthritic pain, pain cannot be eradicated or cured. The goal of therapy is to control pain and to rehabilitate patients so that they can function as well as possible [6]. Single modality treatments are rarely sufficient to manage chronic pain. Management of pain associated with OA and RA usually includes patient education, weight control, physical exercise, cognitive-behavioural strategies, assistive devices, analgesics and anti-inflammatory medications, and surgery [4]. Drug therapy is one of the important components of treatment [6].

Non-steroidal anti-inflammatory drugs (NSAIDs) have been the most widely prescribed therapeutic option for patients with OA and RA [6]. NSAIDs are also the most frequently prescribed drugs for patients with chronic pain and seem to be effective in the management of other chronic disorders [7]. Selective cyclo-oxygenase 2 (COX-2) inhibitors, a new type of NSAIDs, taken orally, are the focus of this report.

EPIDEMIOLOGICAL AND CLINICAL ASPECTS

Chronic pain is a common condition for which patients seek care from various health care providers. It affects hundreds of millions of people worldwide and alters their physical and emotional functioning, decreases their quality of life, and impairs their ability to work. The prevalence of chronic pain varies depending on the study population, definitions, and criteria to define chronic pain [3].

One SR on prevalence rates of chronic pain indicated that rates varied from 10% to 55% [1]. The prevalence of severe chronic pain reported in this SR ranged from 8% in children to 11% in adults [1].

Moulin's study, based on a sample of 2012, indicated that 29% of the Canadian adult population have chronic pain [8], while in a 2003 public telephone survey on health and the health care system in Alberta, 1.4% of the respondents (representative sample of 4000 adult Albertans) reported chronic pain [9].

Recent reports found that the most prevalent disorders associated with chronic pain are RA, OA, and low back pain [10, 11]. These disorders account for about 32% of self-reported cases of chronic pain [10]. Typically, OA affects small joints—hands, feet, neck, back, hips, and knees. RA is a destructive and commonly debilitating systemic inflammatory autoimmune disorder [6].

Arthritis is a leading cause of pain (pain is the cardinal symptom) and the most common cause of long-term disability and health care utilization in Canada [12]. More than four million Canadians or approximately one in six Canadians aged 15 years and over reported having arthritis as a long-term health condition. Two-thirds of those with arthritis are women and nearly three of every five people with arthritis are younger than 65 years of age. By the year 2026, it is estimated that over six million Canadians 15 years of age and older will have arthritis [12].

The prevalence of OA and RA in Alberta and the Northwest Territories is 10% and 1%, respectively [13]. Over 400,000 Albertans live with pain and decreased mobility caused by arthritis and other rheumatic conditions [12, 13].

Chronic pain is considered a major public health issue based on its prevalence and associated consequences [10].

COX-2 INHIBITORS

NSAIDs are widely used for the treatment of musculoskeletal diseases because of their anti-inflammatory and analgesic effects. However, NSAIDs are prescribed with some hesitation due to the possibility of rare but serious upper gastrointestinal (UGI) adverse effects [10, 14-17].

NSAIDs act by interfering with the formation of prostaglandins (PGs) by inhibiting COX enzymes [18]. Since PGs are essential for normal GI, renal, and platelet functions, as well as mediating the inflammatory process, inhibition of the COX enzyme has both beneficial (inhibition of the inflammatory process) and harmful (increased incidence of UGI toxicity: gastroduodenal ulceration, perforation, and bleeding, as well as possible renal and platelet dysfunction) effects.

Two isoforms of the COX enzyme were identified in the late 1980s: cyclo-oxygenase 1 (COX-1) and COX-2. COX-1 is predominantly constitutive and is found in most tissues, particularly in platelets, stomach, and kidney. COX-1 is responsible for the production of PGs, which are responsible for gastroprotection, preservation of renal function during high renin states, and platelet function[19]. COX-2 is predominantly inducible, though it is constitutive in the kidney, brain, testicles, and tracheal epithelia. COX-2 is responsible for the biosynthesis of inflammatory PGs, which lead to redness, heat, swelling, and pain. Its levels can increase 10- to 20-fold in times of inflammation [20, 21].

There are also assumptions that COX-2 inhibitors suppress the formation of prostaglandin I_2 (PGI_2; prostacyclin) in healthy volunteers. PGI_2 seems to be responsible for inhibition of platelet aggregation and vasodilatation. Depression of PGI_2 formation might be expected to elevate blood pressure, accelerate atherogenesis, and predispose patients to an exaggerated thrombotic response to the rupture of an atherosclerotic plaque [22].

Conventional NSAIDs such as naproxen, ibuprofen, and diclofenac are non-selective and inhibit both COX-1 and COX-2 enzymes, thereby providing relief from pain and inflammation, but are associated with UGI events. If drugs inhibit COX-2 but not COX-1 enzymes, then theory predicts the drugs to be analgesics and anti-inflammatory without the adverse effects and events associated with traditional NSAIDs. Theoretically, the advantage of a selective COX-2 inhibitor is that it reduces the signs and symptoms of inflammation and avoids complications caused by COX-1 inhibition [23-25].

Though many COX-2 inhibitors have been introduced recently, the classification of these drugs remains controversial. Different NSAIDs vary in their relative COX-1

and COX-2 selectivity, which is a pharmacological property that has important clinical implications. The capacity of any NSAID to inhibit prostanoid production is expressed as the concentration that inhibits 50% of an enzyme (IC50). The ratio of COX-2 to COX-1 IC50 defines COX-2 selectivity. The smaller the ratio, the more COX-2 selective the drug [26]. Different publications give different relative rank ordering of "COX-2 selectivity" depending on the enzyme source and techniques of performing the test. Table 1 presents information from in vitro studies on the ratio of different NSAIDs, as published by the Oregon Evidence-based Practice Center [27]. The values in the table should be interpreted with caution, considering that different assay methods give different results and no method can predict what will happen when the drug is administered to patients [27].

Table 1: Cyclo-oxygenase selectivity of COX-2 selective and non-selective NSAIDs (in vitro determinations) [27]

NSAID	Ratio
Aspirin	3.12
Naproxen	1.79
Ibuprofen	1.69
Etodolac	0.11
Celecoxib	0.11
Meloxicam	0.09
Diclofenac	0.05
Nimesulide	0.04

Topical NSAID creams may be another way to administer the active substance, but they will not be addressed in this report. A review by the National Institute of Clinical Excellence (NICE) on the efficacy and safety of topical NSAID creams will be available early in 2006.

EVIDENCE FROM SRS

Two SRs (meta-analyses) were located that assessed the effectiveness [19] and safety [19, 21] of celecoxib for non-malignant pain (see Appendix A). Table 2 presents a summary of the reviews, the characteristics reported in these reviews, and the main conclusions by the authors.

Only results from randomized controlled trials (RCTs) were included in the reviews. The methodological quality of the eligible RCTs was assessed in one of the reviews [19]. One review [19] included only patients with RA treated with celecoxib administered orally. Data on the safety of celecoxib were analyzed for patients with OA and RA combined in another review [21]. Data were analyzed in aggregate for both conditions, as there was no evidence of a causal link between the nature of the disease and adverse events (AEs) related to the treatment. The biological plausibility of such a relation is considered to be low [28]. The reviews did not analyze and present data separately for the treatment of chronic and acute pain related to OA and RA.

Several indicators were used to evaluate the efficacy/effectiveness of the drugs in relieving pain, such as the OMERACT outcomes (the number of tender and swollen joints per patient, the patient's and investigator's global assessment) and the ACR-20 index. Safety was assessed by documenting the total number of AEs (UGI complication; perforations, ulcers, and bleeding [PUB], cardiovascular events, edema, hypertension) associated with the therapy and withdrawals associated with total AEs and PUB (see Appendix A).

Table 2: Summary of systematic reviews

Authors, Approach, Number of Studies	Characteristics Reported	Authors' Conclusion
Garner et al. [19] August 2002 **Meta-analysis** approach used for evaluating safety Data analyzed using a fixed effects model **Number of studies:** 5 RCTs published up to August 2002	**Study population:** patients with RA **Comparator:** non-selective NSAIDs (naproxen, diclofenac,) or placebo **Intervention:** celecoxib **Dose intervention:** 80 mg, 200 mg, 400 mg, 800 mg Efficacy: 4 RCTs Safety: 5 RCTs **Age:** >18 years, **gender:** not specified Sample size: >50 in each arm **Follow-up:** at least 4 weeks	**Efficacy:** Celecoxib was equivalent but not superior to naproxen (3 weeks follow-up) and diclofenac (6 weeks follow-up) in the relief of pain. **Safety:** It appeared that up to 6 months of treatment with celecoxib is associated with a lower risk for GI complications but the 52-week results of CLASS suggest that these benefits may not be evident in the long term. There was no evidence on the relative safety profiles of celecoxib and combinations of conventional NSAIDs and gastroprotective agents. There was no evidence to suggest that either the safety or efficacy of celecoxib was dose dependent. There was no evidence to support the practice of co-prescription of a celecoxib and a gastroprotective agent. Celecoxib had no additional benefit in terms of GI safety for patients on low-dose aspirin.
Ashcroft et al. [21] 2001 **Meta-analysis** Approach used for evaluating safety Data analyzed using a fixed effects model **Number of studies:** 5 RCTs published and unpublished up to July 2000	**Study population:** patients with active OA and RA **Comparator:** celecoxib (100 mg, 200 mg, 400 mg daily), non-selective NSAIDs (naproxen, diclofenac, ibuprofen) or placebo **Intervention:** celecoxib **Dose intervention:** 100 mg, 200 mg, 400 mg, 800 mg Safety: 5 RCTs **Age:** not specified; **gender**: not specified Sample size: >200 in each arm **Follow-up:** at least 12 weeks	**Safety:** Endoscopic studies showed that celecoxib at a wide range of doses was well tolerated and associated with a lower incidence of gastroduodenal ulcers compared with naproxen and ibuprofen (12 weeks follow-up), and diclofenac (24 weeks follow-up). The incidence rates of gastroduodenal ulcers associated with celecoxib were similar, although not equivalent to placebo except for celecoxib 400 mg daily, which showed more endoscope ulcers (SS) at 12 weeks follow-up. The differences in incidence of endoscopic gastroduodenal ulcer when compared with different doses of celecoxib (celecoxib 800 mg vs. 100 mg daily; 800 mg vs. 400 mg daily; 400 mg vs. 100 mg daily; 400 mg vs. 200 mg daily; and 200 mg vs. 100 mg daily) was not SS at 12 weeks follow-up.

GI – gastrointestinal; NSAID – non-steroidal anti-inflammatory drug; OA – osteoarthritis; RA – rheumatoid arthritis; RCT – randomized control trial; SS – statistically significant

Efficacy/effectiveness

Celecoxib for patients with RA

Table B.1.1 in Appendix B.1 summarizes the results from one review [19] on the efficacy/ effectiveness of celecoxib, at dosages ranging from 80 mg to 800 mg daily, for the treatment of patients with RA. Only those results (scores, relative risks (RRs), and confidence intervals [CIs]) from RCTs that were clinically and/or statistically significant (SS) are presented in the table. The comparators included in the studies were naproxen 1000 mg daily, diclofenac 150 mg daily, and placebo. The length of follow-up varied from 4 to 24 weeks.

In one trial with a follow-up period of 12 weeks, celecoxib showed significant improvement on all measures, which were greater than those seen in the **placebo** group (SS). There was no dose response found. The 200 mg daily celecoxib was more effective than placebo (SS) for all outcome measures except the physician's global evaluation, the patient's global assessment of disease, and the Health Assessment Questionnaire (HAQ) index. No differences were found in C-reactive protein levels between celecoxib at any dose and placebo. In the other trial included in Garner et al.'s review, with a follow-up of four weeks, no SS difference was found between celecoxib 80 mg daily and placebo for withdrawal that was due to lack of efficacy or on the ACR-20 index assessment. The difference between celecoxib 80 mg daily and placebo on the ACR-20 index was SS only in the first week.

The efficacy was similar for both celecoxib 400 mg daily and **diclofenac** 150 mg daily at 24 weeks follow-up and there were no differences in the number of painful or swollen joints, pain and inflammation, HAQ assessments, ACR-20 index, C-reactive protein, or patient's or physician's global assessment. One trial provided usable data on the comparison of celecoxib 200 mg, 400 mg, and 800 mg daily with **naproxen** 1000 mg daily, for a follow-up period of 12 weeks. The number of withdrawals due to lack of efficacy and the ACR-20 index were not SS different for any doses of celecoxib when compared with naproxen. The only SS difference was a greater improvement measured by the patient's and physician's global assessments with celecoxib 400 mg when compared with naproxen 1000 mg daily. In addition, patients taking 800 mg celecoxib daily obtained a better result (greater improvement) on the HAQ functional disability score.

Safety

Celecoxib for patients with RA and OA

Table B.1.2 in Appendix B.1 summarizes the results from two reviews on the safety of celecoxib for the treatment of patients with OA and RA. In the table, only those results that were clinically and/or SS are presented.

Both reviews [19, 21] synthesized the results from RCTs regarding the safety of celecoxib 200 mg, 400 mg, and 800 mg daily compared with naproxen 1000 mg daily, diclofenac 150 mg daily, ibuprofen 2400 mg daily, and placebo. The review by Garner et al. [19] presented results for patients with RA and the other review [21] presented combined results for patients with either OA and RA. The Celecoxib Long-term Arthritis Safety Study (CLASS) was mentioned in both reviews [19, 21], had the largest sample size (7968 patients), and investigated the incidence of PUB at a follow-up of 26 to 52 weeks. CLASS was not included in the review by Garner et al. [19] because data from OA and RA patients were aggregated. Ashcroft et al. [21] did not mention the reason for excluding the long-term results provided by CLASS from their meta-analysis. In the authors' view, a limitation of their meta-analysis is presentation of safety results from RCTs with short periods of follow-up (12 to 24 weeks) [21].

Total AEs with celecoxib were presented in one review by **Garner et al.** [19]. Only celecoxib at 200 mg daily resulted in more AEs (SS) when compared with **placebo** in patients with RA at 12 weeks follow-up. The results with the other doses, 400 mg and 800 mg daily, were not SS compared with placebo. The results with celecoxib at 200 mg, 400 mg, and 800 mg daily were not SS when compared with **naproxen** 1,000 mg daily for a follow-up period of 12 weeks. The same result (not SS) was reported in a trial that presented combined results obtained from patients with either OA and/or RA treated with celecoxib 400 mg daily and naproxen 1000 mg daily at 12 weeks follow-up. The difference in the safety of celecoxib 400 mg daily was not SS when compared with **diclofenac** at 24 weeks follow-up in patients with RA.

The differences in **withdrawal due to any AE** [19] were not SS for celecoxib at 200 mg, 400 mg, and 800 mg daily when compared with **placebo** and **naproxen** 1000 mg daily at 12 weeks follow-up for patients with RA. The increased safety of celecoxib at 400 mg daily was SS when compared with **diclofenac** 150 mg daily at 24 weeks of treatment. At the same dosage, the difference with celecoxib was not SS compared with **naproxen** in a 12 week study that presented combined results for patients with OA and RA.

The differences in **total GI AEs** [19] were not SS for celecoxib at 200 mg, 400 mg, and 800 mg daily when compared with **naproxen** 1000 mg daily at 12 weeks follow-up for patients with RA. In the same review, another trial showed a similar result when celecoxib 400 mg daily was compared with **naproxen** 1000 mg daily in patients with OA and RA at 12 weeks follow-up. Celecoxib 400 mg daily had SS fewer GI AEs when compared with **diclofenac** 150 mg daily at 24 weeks for patients with RA.

Differences in **withdrawals due to GI AEs** [19] were not SS for celecoxib at 200 mg, 400 mg, and 800 mg daily when compared with **placebo** at 12 weeks. Withdrawals in the groups treated with celecoxib 400 mg and 800 mg were similar to **naproxen**

1000 mg daily at 12 weeks follow-up. Celecoxib 200 mg daily was safer than naproxen 1000 mg daily at 12 weeks follow-up in patients with RA. Difference in celecoxib 400 mg daily was not SS compared with naproxen 1000 mg daily in patients with OA and RA at 12 weeks follow-up. Difference in celecoxib 400 mg daily was SS, and there were fewer GI withdrawals when compared with **diclofenac** in a trial with 24 weeks of follow-up.

Ulcers detected by endoscopy were reported in two reviews [19, 21]. In all studies, the increased safety of celecoxib at different doses, 200 mg, 400 mg, and 800 mg daily (analyzed separately or combined), was found to be SS compared with **non-selective NSAIDs** (naproxen 1000 mg daily, diclofenac 150 mg daily, and/or ibuprofen 2400 mg daily) for 12 to 24 weeks of follow-up in patients with RA and OA.

In the Garner et al. review [19], the incidence of ulceration was the primary end-point. Compared with **placebo**, the risk of developing an ulcer equal to or larger than 3 mm in the groups of patients with RA treated with celecoxib 200 mg, 400 mg, and 800 mg daily was higher but not SS at 12 weeks follow-up. There was no evidence of dose response, but the authors noted that the results must be interpreted with caution because of the high number of patients who did not receive a final endoscopy. A subgroup analysis showed no effect for concurrent aspirin or corticosteroid use, history of GI tract bleeding, or ulcers.

The reduced numbers of both gastric erosion and/or ulcers and duodenal erosion and/or ulcers was found to be SS in the group treated with celecoxib 400 mg daily compared with **diclofenac** 150 mg daily (RA patients) and **naproxen** 1000 mg daily (RA and OA patients) for a follow-up period of 24 and 12 weeks, respectively. If patients were treated with celecoxib at 400 mg daily instead of **diclofenac** for 24 weeks, one patient of seven would have gastric erosion, ulcers, or both, and one patient of 19 would have duodenal erosion, ulcers, or both [19].

In the review by **Ashcroft et al.** [21], the increased safety of **placebo** was found to be SS compared with celecoxib 400 mg daily, but the difference was not SS when compared with celecoxib doses of 100 mg, 200 mg, and 800 mg daily at 12 weeks follow-up for patients with OA and RA. At 12 weeks follow-up, for patients with OA and RA the increased safety of celecoxib at 100 mg, 200 mg, 400 mg, and 800 mg daily was found to be SS compared with **naproxen** 1000 mg daily, when analyzed separately for different doses of celecoxib. The increased safety of celecoxib 400 mg daily was SS when compared with **ibuprofen** 2400 mg daily at 12 weeks follow-up and **diclofenac** 150 mg daily at 24 weeks follow-up for patients with OA and RA.

Ashcroft et al. [21] suggested that there was no obvious dose-related increase in endoscopic ulcers with celecoxib even when twice the maximum recommended dose was used. The same authors specified that the COX-2 enzyme may have a role

in the reparative process of a gastric ulcer. This raises the possibility that a patient who has a pre-existing asymptomatic gastroduodenal ulcer and takes COX-2 inhibitors may be at risk of delaying ulcer healing.

Other safety indicators used by Garner et al. [19] were assessments of peripheral edema and hypertension in patients with RA. **Peripheral edema** was more prevalent in the group treated with celecoxib for a period of four weeks (1% to 2% in celecoxib groups 80 mg, 400 mg, and 800 mg daily) compared with the **placebo** group (no case found). At 24 weeks follow-up, 3% of patients treated with celecoxib 400 mg daily developed edema compared with patients treated with **diclofenac** 150 mg daily, in which the incidence was 2%. The incidence of **hypertension** was 1% in the group treated with celecoxib 400 mg daily and 2% in the group who received diclofenac 150 mg daily. The statistical significance of these results was not reported.

EVIDENCE FROM RCTS

Five RCTs published since July 2002 were located that assessed the efficacy/ effectiveness [29-32] and the safety [17, 30-32] of celecoxib administered to patients who have pain due to OA of the knee and/or hip [17, 29-32] and RA [17] (see Appendix A). The majority of the RCTs that were included focused on populations with chronic pain due to OA and/or RA [17, 29, 30]. However, considering that the SRs did not analyze and present data separately for chronic and acute pain in patients with OA and RA, RCTs that reported results from patients with acute pain (one RCT) [31] and with pain in a flare state (one RCT) [32] were also included.

Table 3 presents a summary of the studies, the characteristics reported, and the main conclusions by the authors. Celecoxib was considered the intervention drug, while the other drugs included in the studies are the comparator drugs. The RCTs differ by their periods of follow-up, which ranged from 15 days [30] to 52 weeks [17]. The efficacy/ effectiveness of the drugs in relieving pain was evaluated by several indicators such as Visual Analogue Scale (VAS), total pain relief over three hours, WOMAC OA index, patient's and physician's assessment of global efficacy, and patient's global assessment of response to therapy. Safety was assessed by documenting the number of total adverse effects such as GI effects (dyspepsia, diarrhea, nausea, flatulence, abdominal pain), central nervous system complaints, skin reaction, and cardiovascular and respiratory effects.

Table 3: Summary of RCTs

Authors, Approach	Characteristics Reported	Authors' Conclusion
Goldstein et al. [17] 2002 USA RCT Study population: Patients randomly included in one of the two protocols (diclofenac protocol) of the Celecoxib Long-Term Arthritis Safety Study (CLASS) who completed the Severity of Dyspepsia Assessment (SODA) questionnaire Sponsored by Pharmacia and Pfizer	**Study population:** patients with either RA and OA ≥ 3 months RA: 27.2% celecoxib, 26.8% diclofenac OA: 72.8% celecoxib, 73.2% diclofenac **Comparator:** non-selective NSAID – diclofenac 150 mg daily **Intervention**: celecoxib 800 mg daily* **Age:** >18 years, mean age 60.5 years **Gender:** female 68.3% celecoxib, 67.2% diclofenac **Ethnicity:** Caucasian: 90.3% celecoxib, 89.6% diclofenac **Sample size:** n_1 = 1997 celecoxib, n_2 = 1996 diclofenac **Follow-up:** baseline, 4, 13, 26, and 52 weeks *Celecoxib 800 mg daily is twice the therapeutic dose for RA and four times that for OA.	**Efficacy:** Not assessed. **Safety:** Celecoxib was superior in all three dimensions of dyspepsia assessed by SODA questionnaire: pain intensity, non-pain symptoms, and satisfaction with dyspepsia-related health at the initial assessment. Changes in dyspepsia-related health occurred within the first 4 weeks of the study and were sustained throughout the observation period. Patients treated with celecoxib reported superior dyspepsia tolerability compared with those treated with diclofenac at standard dosages.
Bianchi and Broggini [29] 2003 Italy **Cross-over RCT**	**Study population:** patients with OA for ≥ 3 months **Comparator:** nimesulide (Aulin®) 100 mg, rofecoxib (Vioxx®)* 25 mg **Intervention**: celecoxib 200 mg **Age:** ≥ 18 years, mean age: 69.0 years **Gender:** not specified **Ethnicity:** not specified **Sample size:** N = 31 patients (one patient withdrew) **Follow-up:** 3 weeks (7 days for each drug) During the washout period (3 days), patients were allowed to take paracetamol 500 mg twice a day but treatment was discontinued at least 24 hours before the study. * Vioxx was withdrawn from the market September 2004.	**Efficacy:** All drugs showed reduction in pain intensity. Nimesulide had a more rapid analgesic action than the other drugs. **Safety:** Results not reported.

Table 3: Summary of RCTs (cont'd)

Authors, Approach	Characteristics reported	Authors' Conclusion
Hawel et al. [30] 2003 Austria RCT Multicentre study (four rehabilitation centres for rheumatic diseases) Sponsored by Gebro Pharma GmbH	**Study population:** patients with OA of the hip (joint pain within the past 3 months) **Comparator:** non-selective NSAID – dexibuprofen 400 mg twice a day **Intervention:** celecoxib 100 mg twice a day **Age:** between 26 and 76 years, mean age 54.2 years **Gender**: 49% female **Ethnicity:** not specified **Sample size:** N = 148 inpatients; n_1 = 74 (celecoxib), n_2 = 74 dexibuprofen **Follow-up:** 15 days Patients were allowed to take low-dose aspirin for non-related indications.	Dexibuprofen has at least equal **efficacy** and a comparable **safety**/tolerability profile as celecoxib in adults with OA of the hip.
Pincus et al. [31] 2004 USA **2 cross-over RCTs** Patient Preference for Placebo, Acetaminophen, or Celecoxib Efficacy Studies (PACES-a, PACES-b)* *In both studies (PACES-a and PACES-b), patients were assigned randomly to receive celecoxib, acetaminophen, or placebo for 6 weeks (treatment period I) followed by a washout period (1 week) and 6 weeks of a second treatment (treatment period II). Sponsored by Pfizer Corporation	**Study population:** patients with OA of the knee and hip (patients with chronic pain syndrome were excluded) **Comparator:** acetaminophen (paracetamol) 1,000 mg four times a day, placebo **Intervention:** celecoxib 200 mg daily **Age:** ≥ 45 years, mean age (range): 51.7 to 68.4 years (PACES-a) and 62.7 to 64.8 (PACES-b) **Gender** (range %): female 51.7 to 68.4 (PACES-a) and 57.1 to 71.4 (PACES-b) **Ethnicity** (range %): Caucasian 84.2 to 90.1 (PACES-a) and 79 to 90.8 (PACES-b) **Sample size:** N = 524 patients (PACES-a), N = 556 patients (PACES-b) **Follow-up:** five visits during 14 weeks Propoxyphene (Darvon) 65 mg up to four times daily or codeine (Ultram) 100 mg up to four times daily were allowed as rescue medication but patients were instructed not to take these drugs within 12 hours of any visit.	**Efficacy:** Celecoxib was superior to acetaminophen and placebo. **Safety:** The adverse effects and tolerability were similar for the intervention and comparator drugs

Table 3: Summary of RCTs (cont'd)

Authors, Approach	Characteristics reported	Authors' Conclusion
Gibofsky et al. [32] 2003 USA **RCT** Multicentre study (61 centres in the United States and Canada) Sponsored by Pharmacia Corporation	**Study population:** patients with OA of the knee in a flare state, with duration of OA (mean range) 8.3 to 8.8 years **Comparator:** rofecoxib* (R) 25 mg daily, placebo (P) **Intervention:** celecoxib (C) 200 mg daily **Age:** ≥ 40 years, mean age years: 62.2 (C), 63.4 (R), 63.1 (P) **Gender:** female (%): 69 (C), 66 (R), 65 (P) **Ethnicity:** not specified **Sample size:** N = 475 patients n_1 = 189 (C), n_2 = 190 (R), n_3 = 96 (P) **Follow-up:** 6 weeks Patients were allowed to take low-dose aspirin (≤ 325 mg daily) for cardiovascular prophylaxis and acetaminophen and antacids, which had to be discontinued for 48 hours prior to the arthritis assessment. * Rofecoxib (Vioxx®) was withdrawn from the market September 2004.	**Efficacy:** Celecoxib 200 mg daily and rofecoxib 25 mg daily are equally efficacious in treating the signs and symptoms of OA and are superior to placebo (SS). **Safety:** All treatments were tolerated, with similar proportions of patients withdrawing due to adverse effects.

NSAID – non-steroidal anti-inflammatory drug; OA – osteoarthritis; RA – rheumatoid arthritis; RCT – randomized control trial; SS – statistically significant

Efficacy/effectiveness

Celecoxib for patients with OA

The table B.2.1 in Appendix B.2 summarizes the results from four RCTs. A reduction in pain was obtained with celecoxib and active comparator drugs nimesulide, dexibuprofen, and acetaminophen. In two RCTs [29, 32] the comparator was rofecoxib (Vioxx®), a COX-2 inhibitor that was withdrawn from the market in September 2004.

In one RCT by **Bianchi and Broggini** [29], **nimesulide** (Aulin®), a COX-2 inhibitor, at a dosage of 100 mg daily, showed a SS better analgesic effect compared with celecoxib 200 mg daily for the treatment of patients with OA of the knee for more than three months, although the pain assessment after one week of treatment provided similar results for the VAS scores with all drugs (celecoxib, nimesulide, and rofecoxib 25 mg daily). Each treatment was administered for a period of one week.

In another RCT by **Hawel et al.** [30], **dexibuprofen** (an isolated active enantiomer of ibuprofen) at 800 mg daily showed comparable results to celecoxib 200 mg daily in adults with OA of the hip with joint pain within the past three months. There were no SS differences for all efficacy criteria assessed such as the WOMAC OA index, different categories of pain, handicap, restriction of movement, and quality of life during the follow-up period of 15 days. Also, there were no differences in the judgement of the efficacy of the treatment by physicians and patients between celecoxib and dexibuprofen.

Pincus et al. [31] presented results from two multicentre cross-over RCTs on patient preferences for placebo, acetaminophen, or celecoxib (PACES-a and PACES-b). Patients with chronic pain syndrome were not included in the studies. Patients were assigned randomly to one of six treatment sequence groups and received a sequence of two of three treatments. Each drug was administered for 6 weeks with a washout period of 1 week between the two treatment periods. The total follow-up period was 14 weeks. The efficaciousness of celecoxib 200 mg daily was SS higher compared with **acetaminophen** 1000 mg four times a day and that of acetaminophen was SS higher compared with **placebo** in patients with OA of the knee and hip. In both periods of the studies, with the exception of Period I of PACES-a, when no SS differences between celecoxib and acetaminophen and between acetaminophen and placebo were indicated, the differences between celecoxib and placebo were significant for the WOMAC and pain VAS scores. In both studies, the higher number of patients who preferred celecoxib compared with acetaminophen was SS (53% versus 24% in PACES-a [$p < 0.001$], and 50% versus 32% in PACES-b [$p = 0.009$]).

In the multicentre study by **Gibofsky et al.** [32], with a follow-up of 6 weeks, celecoxib 200 mg daily was compared with **rofecoxib** 25 mg daily and **placebo** in patients with OA of the knee in a flare state. The analysis of results was based on an intention-to-treat model. The primary measures of efficacy were the patient's assessment of arthritic pain on the VAS (OA pain) and the WOMAC scores at week 6. Secondary measures included the patient's and physician's global assessment, the patient's assessment of arthritic pain on the VAS (pain on walking), and WOMAC scales for pain, stiffness, and physical function. Both active treatments showed the same SS better efficacy compared with placebo ($p \leq 0.016$). Withdrawals due to treatment failure were 5% in both active treatment groups and 22% in the placebo group.

Safety

Celecoxib for patients with OA and RA

The table B.2.1 in Appendix B.2 summarizes the results from four RCTs.

The study by **Goldstein et al.** [17], with a follow-up of 52 weeks, included patients with OA and RA who participated in CLASS, received treatment with either diclofenac or celecoxib, and completed the Severity of Dyspepsia Assessment (SODA) questionnaire. Patients treated with celecoxib at two to four times the maximum recommended dose (800 mg daily) reported superior dyspepsia tolerability compared with those treated with **diclofenac** at standard dosages of 150 mg daily (pain intensity [$p < 0.001$], non-pain symptoms [$p = 0.005$] at four weeks but not at weeks 13, 26, and 52 [$p = 0.12$ and $p > 0.20$], and satisfaction with dyspepsia-related health at the initial assessment [$p = 0.001$]). Patients treated with celecoxib had a lower overall incidence of any GI adverse effect compared with diclofenac (40.4% versus 48.1%, respectively [$p < 0.001$]). Also, the patients treated with celecoxib experienced lower rates for specific GI adverse effects (dyspepsia [$p = 0.053$], abdominal pain [$p < 0.001$], diarrhea [$p = 0.001$], nausea [$p < 0.001$], constipation [$p < 0.001$], and flatulence [$p = 0.094$]). The higher number of patients treated with diclofenac who withdrew due to any GI adverse effect was SS compared with placebo ($p < 0.001$). The time at which the incidence of GI AEs and the statistical significance of the results were measured is not stated.

In the RCT published by **Hawel et al.** [30], the overall incidence of adverse effects was 12.16% in the group of patients treated with **dexibuprofen** 800 mg daily and 13.51% in the group treated with celecoxib 200 mg daily, during a follow-up period of 15 days. The most prevalent adverse effects in the dexibuprofen group were six GI complaints, two central nervous system complaints, and one skin reaction, while in the celecoxib group, the most prevalent adverse effects were seven GI complaints, one skin reaction, and one cardiovascular complaint. The authors concluded that

dexibuprofen has a similar safety profile to that of celecoxib in adults with OA of the hip.

Pincus et al. [31] presented results for patients with OA of the knee and hip, treated with celecoxib 200 mg daily, **acetaminophen** 4000 mg daily, and **placebo**. No SS differences were found between the proportion of patients reporting any GI adverse effect (diarrhea, dyspepsia, nausea, and flatulence), upper respiratory infection, or headache for any treatment drug and placebo.

In the **Gibofsky et al.** [32] RCT, all treatments (celecoxib 200 mg daily, rofecoxib 25 mg daily) and placebo were considered to be well tolerated. The incidence of any adverse effect was similar for both the celecoxib and **rofecoxib** groups (43% and 42%, respectively). In the **placebo** group, the reported proportion of patients who experienced any adverse effect was 30%. During the 6 weeks of follow-up, the most common adverse effects with celecoxib were headache, dyspepsia, diarrhea, peripheral edema, rhinitis, abdominal pain, and sinusitis. Hypertension was found in one patient in the celecoxib group compared with six patients in the rofecoxib group. The proportions of withdrawal due to adverse effects were 6% in the celecoxib group and 5% in both the rofecoxib and placebo groups.

Information on the safety of celecoxib from CLASS

Silverstein et al. [33] published results from the largest and longest randomized double-blind trial on GI toxicity with celecoxib versus NSAIDs administered to patients with OA and RA. In CLASS, celecoxib 800 mg daily (two and four times the maximum Health Canada [HC] and Food and Drug Administration [FDA] approved effective dosage for RA and OA) was compared with **diclofenac** 150 mg daily and **ibuprofen** 2400 mg daily. A total of 8059 patients were enrolled in the study, but only 4573 patients (57%) received treatment for six months. More than 20% of the patients were taking low-dose aspirin (≤325 mg daily) and patients with a recent history of gastroduodenal ulcers were excluded. The study end-points were incidence of symptomatic UGI ulcers, ulcer complications (perforation, obstruction, and bleeding), and other adverse effects. No differences were found in the incidence of cardiovascular events between celecoxib and non-selective NSAIDs, irrespective of aspirin use.

FDA's review of CLASS results by **Goldkind** [34] emphasized that there were no SS differences in the number of complicated ulcers between the celecoxib and NSAID groups of patients when results were analyzed in combination or individually. The composite end-point of symptomatic and complicated ulcers suggested a difference between celecoxib and ibuprofen in favor of celecoxib but no difference between celecoxib and diclofenac. Co-administration of aspirin was associated with an increased and similar risk of complicated ulcers and of the combined symptomatic and complicated ulcers in both celecoxib and diclofenac groups. Interestingly, the

ibuprofen patients who received low-dose aspirin experienced a lower rate of complicated ulcers. In the reviewer's opinion, the result obtained in this group of patients may represent a random finding or a true differential interaction between aspirin and NSAIDs in terms of UGI toxicity. No conclusions regarding the safety of celecoxib compared with traditional less selective COX-2 inhibitors as a group were possible and further study was suggested to clarify the safety of co-administration of aspirin and selective and non-selective NSAIDs.

REGULATION STATUS AND POST-MARKETING DATA

Health Canada and FDA regulatory status

Celecoxib (Celebrex®), the focus of this report, was approved by HC and the FDA in the late 1990s. Table 4 presents the regulatory status, the approved indications for use, and the recommended dosages for patients with OA and RA. Other COX-2 inhibitors—meloxicam (Mobicox®), and Etodolac (Apo®-, Gen-, and Taro-)—are also approved by HC.

Table 4: Licensure and indications in Canada and the United States

	Celecoxib (Celebrex®)
Supplied and approval date by HC[a]	100 mg – approved 1999 200 mg – approved 1999 400 mg – not approved 2003
Supplied and approval date by FDA[b]	100 mg – approved December 1998 200 mg – approved December 1998
Indication HC[c]/FDA[b]	Acute and chronic use in the relief of the signs and symptoms of OA and RA in adults
Recommended dosage (OA/RA) HC[c]	**OA**: 200 mg single dose or two divided doses **RA**: Starting dose: 100 mg twice daily; may be increased to 200 mg twice daily as needed

COX-2 – cyclo-oxygenase 2; FDA – Food and Drug Administration;
HC – Health Canada; OA – osteoarthritis; RA – rheumatoid arthritis

[a] Information obtained from the Submission and Information Policy Division Therapeutic Products Directorate, HC
[b] Information obtained from http://www.fda.gov (accessed 02.06.2004)
[c] Information obtained form *Compendium of Pharmaceuticals and Specialties (CPS)*, the Canadian drug reference for health professionals, 2004

Rofecoxib (Vioxx®), a COX-2 selective inhibitor used widely for control of pain associated with OA and RA, has been available on the market since 1999. As of September 30, 2004, Merck & Co Inc. decided to withdraw rofecoxib from the market. The decision was based on results obtained from a three-year prospective, randomized, placebo-controlled clinical trial (APPROVe – Ademomatous Polyp Prevention Vioxx®) that enrolled 2600 patients with a previous history of colorectal adenoma. The trial was designed to determine if Vioxx® could prevent recurrence of colon polyps, which can become cancerous. After 18 months of treatment, patients taking rofecoxib 25 mg daily were at twice the risk of having a heart attack and stroke compared with those receiving the placebo [35-37].

As a result, HC, the US FDA and the European Medicine Agency stated that they would continue to study the long-term effects of COX-2 inhibitors to establish if the cardiovascular effects were related only to this drug or to the entire class of COX-2 inhibitors [38, 39].

Labeling and public health alerts in the United States, Canada, and Australia

The NSAID-class warning issued by the FDA regarding the potential risk of an adverse GI event continues to be included on the labels of celecoxib. This warning refers to the administration of the lowest effective dose for the shortest possible duration [40, 41]. Because of the lack of platelet effects, celecoxib is not a substitute for aspirin, which is required for cardiovascular prophylaxis. Celecoxib can be used with low-dose aspirin; however, concomitant administration may result in an increased rate of GI ulceration or other complications.

Prospective long-term studies specifically designed to compare the incidence of serious cardiovascular events in patients taking COX-2 inhibitors versus non-selective NSAIDs or placebo have not been conducted [41]. Because of the recent information about cardiovascular risks associated with COX-2 inhibitors, the National Institutes of Health in the United States evaluated three large preventive ongoing studies. Based on this evaluation, the National Cancer Institute stopped a 3-year celecoxib study (Adenoma Prevention with Celecoxib) that aimed to evaluate the effectiveness and the safety of celecoxib in reducing the risk of colon polyps. Preliminary data showed a SS increase in the risk of cardiovascular events (cardiovascular death, acute myocardial infarction, and stroke) in patients randomized to celecoxib after 2.8 years of follow-up. Patients taking celecoxib 200 mg twice a day had a 2.5-fold increase in cardiovascular events compared with placebo. Also, celecoxib at 400 mg twice a day showed a 3.4-fold increase in cardiovascular events compared with the placebo group.

In December 2004, HC informed Canadians of safety concerns regarding COX-2 inhibitors, including celecoxib, and advised patients to discuss the benefits and risks of treatment options with their physicians. Also, HC has requested additional safety information from the manufacturers of these drugs and will continue to review the safety profile of COX-2 inhibitors available on the market [42].

Following these findings, the FDA issued an alert for practitioners which specified that their patients should be informed about the possible cardiovascular risk associated with celecoxib. The alert stated that alternative treatments must be considered for individual patient needs and risk factors, and the lowest effective dose of the drug should be used in cases where an alternative is not acceptable [43].

Australia's Therapeutic Goods Administration informed all manufacturers of COX-2 inhibitor drugs in February 2005 to place a warning label on their drugs about an increased risk of cardiovascular problems. They also advised patients who take more than 200 mg a day of celecoxib to discuss their treatment regimen with their physician [44].

Based on the ongoing scientific review of the cardiovascular safety of selective COX-2 inhibitors, HC recommended important new usage restrictions for Celebrex® beginning in April 2005. Celebrex® should not be used in patients who have had a heart attack or stroke, serious chest pain related to heart disease, or congestive heart failure. Celebrex® may increase the risk of cardiovascular events in patients with significant risk factors for heart attack and stroke such as high blood pressure, high cholesterol, diabetes, and smoking. Patients in this group are advised to consider other treatments. Celebrex® should be prescribed and used at the lowest possible dose and for the shortest, necessary period of time [45]. Also, HC requested Pfizer Canada Inc. to voluntary discontinue sales of valdecoxib (Bextra®), based on information about serious, potentially life threatening skin reactions [45].

Post-marketing data in Canada

HC published a report in April 2002 indicating that the number of adverse reactions associated with celecoxib was 528 from the date the drug was marketed to October 12, 2001. There were 70 suspected cardiovascular and cerebrovascular adverse reactions associated with celecoxib. These figures were based on spontaneous post-marketing reports, which are generally presumed to underestimate the risks associated with drug treatments [18]. There was no specification regarding the medical condition (OA, RA, or other) of patients who developed those adverse reactions [18].

A population-based cross-sectional time-series analysis using administrative health care databases including more than 1.3 million residents of Ontario, Canada, aged at least 66 years, was done to examine temporal changes in the use of NSAIDs and upper GI haemorrhage hospitalization rates after the introduction of COX-2 inhibitors. The study referred to celecoxib and rofecoxib and covered the period from September 1, 1994, to February 28, 2002. Celecoxib and rofecoxib were introduced on the provincial drug formulary in April 2000 [46].

The prevalence rate of use of NSAIDs among Ontario's population of older people increased from 14.0% just before the introduction of COX-2 inhibitors to 19.8% by the end of the observation period ($p < 0.01$). These rates represent an absolute increase of more than 90,000 additional individuals annually using NSAIDs, attributable mainly to the use of COX-2 inhibitors rather than switching from non-selective NSAIDs to COX-2 inhibitors. The rate of hospitalization for upper GI

haemorrhage increased from about 15.4 to 17.0 per 10,000 older persons after the introduction of COX-2 inhibitors ($p < 0.01$). This represents an absolute increase of more than 650 upper GI haemorrhage hospitalizations annually. The 41% rise in NSAID use, due to increased use of COX-2 inhibitors, was accompanied by a 10% increase in hospitalization rates for upper GI haemorrhage. The results of this ecological study, however, cannot prove causation. The authors concluded that even if a new drug is associated with lower side effects than previous drugs in its class at the patient level, a marked increase in its use can be associated with an apparently paradoxical adverse impact on the population [46].

POSITION PAPERS AND GUIDELINES

A summary of position papers and guidelines issued by national bodies in Canada, the United Kingdom, and the United States on the use of COX-2 inhibitors for the treatment of RA and OA is presented in Table 5. No formal assessment was carried out to determine if these guidance documents were based on research evidence, and, if so, whether they were based on the same research evidence.

Clearly there are differences among the recommendations from the three national bodies. Both the guidance documents from the Canadian Consensus Conference and NICE in the United Kingdom agree that COX-2 inhibitors are preferred in patients with RA and OA who are at *"high risk"* for serious GI adverse effects. However, the recommendation on the general use of NSAIDs and COX-2 selective inhibitors differs in all three.

NICE has issued a holding statement relating to their guidance on COX-2 inhibitors [47] following the withdrawal of rofecoxib from the market. The NICE guidance continues to apply to the other COX-2 inhibitors [48]. The updated review of the guidance will no longer include rofecoxib, and the expected date for issue is May 2005 [49].

The National Guideline Clearinghouse has withdrawn and/or modified the guideline summaries that make recommendations for the use of rofecoxib for the management of RA, OA, and management of pain [50].

The European League Against Rheumatism (EULAR) published updated recommendations for the treatment of OA of the knee in 2003 [51]. The recommendations are based on the results of a systematic search of the literature published up to February 2002, which included all treatments and were based on expert opinion. Acetaminophen (paracetamol) was considered to be the analgesic for first-line therapy and use for the long term. NSAIDs should be considered in patients unresponsive to paracetamol. In patients with an increased GI risk, non-selective NSAIDs and effective gastroprotective agents or selective COX-2 inhibitors should be used [51].

Table 5: Position papers and guidelines on the use of COX-2 inhibitors for RA and OA

Position Paper/ Guideline	Evidence-based approach to prescribing NSAIDs in the treatment of RA and OA [52]	Guidance on the use of cyclo-oxygenase 2 (COX-2) selective inhibitors celecoxib, rofecoxib, meloxicam, and etodolac for OA and RA [47]	Guideline for the management of pain in OA, RA, and juvenile chronic arthritis [6]
Country, Issued Institution, Year of Publication	Canada The Second Canadian Consensus Conference (Canadian specialists and family physicians) 2000	UK National Institute for Clinical Excellence (NICE) 2001	US American Pain Society (APS) 2002
Recommendations	NSAIDs (including COX-2 selective inhibitors) should be the drugs of choice for the symptomatic treatment of patients with RA and moderate to severe OA. The COX-2 selective inhibitors are the treatment of choice in patients with risk factors for PUB. The use of all NSAIDs including COX-2 selective inhibitors should be avoided, if possible, in patients who have had UGI bleeding within the past 4 to 6 weeks. If COX-2 use is unavoidable, proton pump inhibitors or misoprostol should be co-administered.	COX-2 selective inhibitors are not recommended for routine use in patients with RA and OA. COX-2 should be used in preference to standard NSAIDs only in patients with RA and OA who may be at "high risk" of developing serious GI adverse effects. "High-risk" patients: ≥ 65 years; concomitant medications known to increase the likelihood of UGI adverse events; serious co-morbidity (cardiovascular disease, renal or hepatic impairment, diabetes, and hypertension); require the prolonged use of the maximum recommended dose of standard NSAIDs. The risk of GI complications is particularly increased in patients with previous clinical history of gastroduodenal PUB.	COX-2 selective NSAIDs are the first choice for a patient with OA and moderate to severe pain and/or inflammation, unless the patient is at significant risk for hypertension or renal disorder. For the patient with active RA and moderate to severe pain, a COX-2 selective NSAID should be used together with disease modifier anti-rheumatic drugs (DMARDs), as a concomitant medication, unless there are clear risk factors for exacerbation of renal disease or the medications are not tolerated due to GI complications.
Co-administration of Aspirin and COX-2 Inhibitors	Low-dose aspirin can be used concurrently for vascular prophylaxis. However, neither traditional NSAIDs nor COX-2 specific inhibitors can be substituted for aspirin.	There is no evidence to justify the use of COX-2 over standard NSAIDs in patients with cardiovascular disease who are on low-dose aspirin. Low-dose aspirin reduced the benefit (to decrease the GI problems) of a COX-2 selective drug.	A regular low dose of aspirin (75 mg to 160 mg daily) should be given to patients with OA and/or RA at risk for a cardiovascular event, whether the patient is treated with a non-selective or COX-2 selective NSAID.

GI – gastrointestinal; NSAID – non-steroidal anti-inflammatory drug; OA – osteoarthritis; PUB – perforations, ulcers, and bleeding; RA – rheumatoid arthritis; UGI – upper gastrointestinal

COST AND MARKETING

The costs of COX-2 inhibitors are higher than traditional NSAIDs. Celecoxib is twice as costly as non-selective NSAIDs [53].

The NICE report indicated that the annual drug costs in 2001 of rofecoxib and celecoxib for patients with OA and RA was £109.8, as compared with the cost of generic traditional NSAIDs at £54.0 [54]. It was estimated that switching high-risk OA and RA patients to COX-2 selective inhibitors would lead to an annual incremental cost of approximately £25 million to the National Healthcare System.

In Canada, the price difference between the one-month treatment with a generic non-selective NSAID ibuprofen (Cdn $12-13), diclofenac (Cdn $27), or naproxen (Cdn $16-20) and a selective NSAID celecoxib (Cdn $52-97) is in the range of Cdn $40-80 for ibuprofen, Cdn $10-50 for diclofenac, and Cdn $25-50 for naproxen [55]. The price for 1 month's treatment with Arthrotec® (combination diclofenac and misoprostol drug), a drug used to prevent ulcers in patients who take certain arthritic and pain medications, is Cdn $47-61. This cost is approximately comparable to the cost of a COX-2 inhibitor [55].

The introduction, marketing, use, and post-marketing experience of COX-2 specific inhibitors have produced dramatic changes in the US market. Celecoxib was first introduced into the market in January 1999 [56]. International Marketing Service Health reported in June 1999 that in the first 10 days of prescription activity, 3231 prescriptions for celecoxib (Celebrex®) were dispensed in the United States [56]. At 15 weeks post-launch, the total number of Celebrex® prescriptions dispensed in the United States had reached 3.2 million. It is estimated that Americans spend US $6 billion a year for arthritic pain drugs such as celecoxib and rofecoxib [57].

Prior to the introduction of COX-2 inhibitors in Canada, the total number of NSAID prescriptions dispensed by pharmacies was 9 million in 1998. In 2001, 14 million prescriptions were dispensed—6 million for conventional NSAIDs and 8 million for COX-2 inhibitors [58]. In 2001, celecoxib ranked seventh in the top 200 prescribed medications in Canada [59].

IMS Health Canada published on its web site a table that shows the estimated number of prescriptions dispensed for anti-arthritics (COX-2 selective inhibitors and other NSAIDs) by Canadian Retail Pharmacies, for the time period 1999 to February 2005. Between 2000 and 2004, the estimated number of prescriptions dispensed for Celebrex® was characterized by fluctuations. After reaching the highest value of 3,796,386 prescriptions in 2000 (representing a mean of 316,366 prescriptions per month) the number of prescriptions decreased continually in the following years, with the lowest number of prescriptions (2,961,856) recorded in 2003. This decrease

in numbers was also observed throughout 2004 except for the month of October when an increase was probably related to the withdrawal of Vioxx® from the market in September. In February 2005 the estimated number of prescriptions for Celebrex® was 150,546 representing approximately half of the prescriptions dispensed per month in 2000. The prescriptions dispensed for all COX-2 selective inhibitors showed the same fluctuations with a pronounced and continuous decrease in the months following the withdrawal of Vioxx® by Merck. A constant decrease in the number of prescriptions dispensed for other NSAIDs was noted during 2000 to 2004. Interestingly, after the September 2004, patients were switched to other anti-arthritics, such as older NSAIDs [60].

Prescribing patterns in Canada, however, are dictated by the provincial coverage plans. A report published in November 2003 analyzed the effect/impact of provincial drug plan coverage policies for new drugs on patterns of use (in persons aged 65 years and older) and cost in two provinces, Ontario and British Columbia (BC) [61]. Conventional NSAIDs were covered in both provinces as general benefit drugs.

In Ontario, COX-2 inhibitors were covered under the limited use (LU) program while in BC they were covered as special authority (SA) program drugs. In Ontario, quarterly oral NSAID use per senior rose by 70% in the year following approval of COX-2 inhibitors (celecoxib and rofecoxib) as LU products, leading to a near tripling of quarterly NSAID costs. In contrast, there was virtually no increase in NSAID utilization or provincial drug plan cost per senior when COX-2 inhibitors were granted SA status in BC. These results highlight the impact of the early, rapid uptake of COX-2 inhibitors in Ontario versus an apparently lower, more sustained level of use among BC seniors, as reflected by prescriptions paid by the provincial drug plans [61].

Homik and Suarez-Almazor [62] reviewed economic analyses on COX-2 inhibitors for the treatment of patients with *"arthritis"*. The results of the cost-effectiveness analyses identified varied from review to review. Some reviews showed cost savings, while others calculated a significant cost in order to achieve any change in quality of life. From the findings, the authors concluded that COX-2 inhibitors represent a cost-effective solution to treating a patient at high risk for serious GI events, although the increased efficacy comes with increased costs. Using COX-2 inhibitors instead of traditional NSAIDs in low-risk patients was not found to be cost-effective in two cost-utility analyses. There were still unanswered questions regarding the costs and consequences (in terms of efficacy and GI risk reduction) when low-dose aspirin or proton pump inhibitors were used concurrently.

DISCUSSION

SRs on celecoxib

In Appendix C a comparative table of both included and excluded SRs lists all of the RCTs on celecoxib that were included in each of the SRs. When comparing the RCTs analyzed in the excluded and included SRs chosen for this report, the majority of RCTs selected and assessed in all of the SRs were the same.

The authors used different criteria for selecting RCTs and different ways to analyze and present results. These methodological variations may account for some of the differences observed.

Efficacy/effectiveness of celecoxib was measured by evaluating both pain reduction and functional improvement. The daily dosages of celecoxib varied from 80 mg to 800 mg and were compared to placebo, naproxen (1,000 mg), and diclofenac (150 mg) over a period of 3 to 6 months for patients with RA. At 3 months follow-up, celecoxib at any dose showed SS improvement compared with placebo. At 400 mg daily for 3 months, celecoxib, when compared with naproxen, showed SS improvement only on the patient's and physician's global assessments. At 6 months, celecoxib 400 mg daily was just as effective as diclofenac (150 mg).

Overall, the short-term use of celecoxib (a selective COX-2 inhibitor) is equivalent to non-selective NSAIDs (naproxen, diclofenac) in reducing pain and improving function for patients with RA.

The safety profile is somewhat more complex, depending on the outcome measure used. As determined by endoscopic evaluation, the number of gastroduodenal erosions or ulcers were significantly reduced in RA and OA patients after taking 400 mg daily of celecoxib compared with diclofenac (150 mg daily) after six months and naproxen (1000 mg daily) and ibuprofen (2400 mg daily) after three months. The incidence of peripheral edema was slightly higher in the celecoxib group (3%) compared with the diclofenac group (2%) at six months.

In summary, short-term use of celecoxib results in a reduction in gastric/duodenal erosions or ulcers compared with non-selective NSAIDs (naproxen, ibuprofen, and diclofenac) for patients with RA and OA.

RCTs on celecoxib

RCTs focused on the efficacy/effectiveness of celecoxib at 200 mg administered daily for the treatment of OA and on the safety of celecoxib (200 mg and 800 mg daily) for the treatment of OA and RA.

RCTs were also characterized by variability in such methodological details as comparators (selective and non-selective NSAIDs and placebo; also, in one RCT, the

comparator was an analgesic drug [acetaminophen], which is not an NSAID, but a drug recommended by EULAR to try first in patients with OA of the knee), sample size and characteristics of the patients involved, periods of follow-up, and measurement of outcome.

Overall, short-term use of celecoxib 200 mg daily showed the same efficacy when compared with different active drugs (COX-2 inhibitors: nimesulide 100 mg daily and rofecoxib 25 mg daily, or dexibuprofen 800 mg daily), was superior to acetaminophen 1000 mg four times a day, and provided a SS improvement when compared with placebo in patients with OA.

The safety analyses indicated that celecoxib 800 mg daily (dosage representing two to four times the maximum recommended dose) was superior in dyspepsia tolerability compared with diclofenac 150 mg daily (standard dosage). Celecoxib 200 mg daily showed a similar safety profile when compared with other active treatments (selective and non-selective NSAIDs). The results did not provide information on the safety profile at different dose regimes. None of the RCTs included in the review investigated gastroduodenal erosions or ulcers.

Based on a review of CLASS by the FDA, no conclusions on the safety of celecoxib compared with traditional NSAIDs as a group were possible and research was called for on the safety of co-administration of aspirin.

Future research

Many questions remain to be addressed. In one review [21], the authors presented a possible role for the COX-2 enzyme in the reparative process of a gastric ulcer. If this is the case, patients with pre-existing asymptomatic ulcers taking COX-2 selective inhibitors including celecoxib may be at risk of delayed ulcer healing. This was also the subject of concern for the FDA, as specified in one RCT [30]. Without warning symptoms, there may be an increase of ulcer-related complications [30].

There was no information available in the reviews and RCTs to determine whether the use of celecoxib may result in fewer GI AEs compared with a combined treatment of non-selective NSAIDs and drugs such as proton pump inhibitors or H2 antagonists that can protect the stomach or intestine. In addition, there is a lack of research studies that compare GI AEs in high-risk patients such as those who chronically use corticosteroids and who also take celecoxib or non-selective NSAIDs. In three RCTs, recent treatment with corticosteroids was one of the exclusion criteria for entering patients into the trial [30-32].

Future studies need to use improved outcome definitions of drug-induced ulcer complications and to investigate other possible outcomes. The studies need to be

large and to include groups of patients at high risk and for longer periods of follow-up. Post-marketing surveillance is needed to determine the risk-benefit profile of celecoxib.

Aspirin may prevent cardiovascular disease but also may increase the risk of GI complications. In two RCTs [30, 32] patients were allowed to take low-dose aspirin for non-related indications and for cardiovascular prophylaxis, respectively. However, the authors did not analyze and present the results based on this fact. Because of the unknown effect of the co-administration of aspirin, in all of the reviews [19, 21], the authors concluded that more studies are needed to confirm the effects of taking COX-2 inhibitors and low doses of aspirin for cardiovascular prophylaxis. These concerns were also echoed in a larger study that showed an apparent absence of any benefit of celecoxib over non-selective NSAIDs when aspirin was co-administered with celecoxib [33].

Furthermore, there is a need for a robust cost-effectiveness analysis before new drugs are covered by provincial drug plans. A limited Canadian survey showed that the introduction of COX-2 inhibitors (celecoxib and rofecoxib) in the market was associated with an increase in prescriptions as a consequence of the coverage policies and their level of restrictiveness [61]. It seems that physicians tend to prescribe drugs with fewer side effects even if the decrease in side effects is small and the increase in price is large [63].

Presently, there are 57 ongoing trials with celecoxib and researchers are currently recruiting patients. A number of these trials will be exceeding 18 months of follow-up as specified in the US National Institutes of Health Clinical Trials registry [64]. These studies, however, are mainly in the field of oncology [65].

Clinical relevance

In general, from the available information in this report, there is no evidence to support the view that the safety and efficacy of celecoxib is dose dependent when used in the short term (less than 6 months).

Celecoxib is approved by HC and the FDA to be used for the treatment of adult patients with OA and RA. The recommended daily dosage (Compendium of Pharmaceuticals and Specialties, Canada) for patients with OA was a 200-mg single dose or two doses of 100 mg. The recommended dosage for patients with RA is 100 mg twice daily to a maximum of 200 mg twice daily as needed. The studies included in the SRs assessed a wide range of dosages and in some cases exceeded the recommended dose.

Regarding the indications, the views are different. The APS (2002) recommended COX-2 selective NSAIDs to be the first choice of treatment for patients with OA and RA with moderate to severe pain unless the patient is at significant risk for hypertension or renal disorder. The Canadian Consensus Conference (2000) shared a similar opinion but expanded the indication to any NSAIDs including COX-2 selective inhibitors; however, COX-2 inhibitors were recommended as the treatment of choice in patients at risk for PUB. On the other hand, NICE (2001) does not recommend COX-2 selective inhibitors for routine use in patients with RA and OA, only in patients at high risk of developing GI AEs. Furthermore, the APS recommends that patients with RA should use disease modifier anti-rheumatic drugs in combination with COX-2 selective NSAIDs.

The recommendations from the Canadian Consensus Conference [52] considered that low-dose aspirin can be used concurrently with NSAIDs for vascular prophylaxis. The Clinical Guidance from APS [6] also recommended that patients at risk for cardiovascular event should be given low-dose aspirin regularly. NICE guidance [47] was not very clear on concurrent administration of aspirin.

Some recent long-term studies involving patients with conditions other than OA and RA showed that treatment with COX-2 inhibitors might be associated with an elevation of blood pressure, acceleration of atherogenesis, and acceleration of a thrombotic response. Recently, the National Health Institute in the United States evaluated the preliminary results from three large preventive studies in progress, and, from the findings and the increased risk of cardiovascular events, the National Cancer Institute terminated a 3-year celecoxib study that involved patients with conditions other than OA and RA (Adenoma Prevention with Celecoxib) [43].

COX-2 inhibitors, including celecoxib, remain the choice of drug for patients at low cardiovascular risk but who have had serious GI events, especially while taking traditional NSAIDs. It seems to be prudent to avoid COX-2 inhibitors in patients who have cardiovascular disease or who are at risk for it [22].

When examining adverse effects of treatment, the number needed to harm (NNH) may be the most useful clinical presentation. Figure 1 mainly provides the outcome of endoscopic evaluations to determine the presence of ulcers. These are point estimates and have some uncertainty around them.

Figure 1: Number Needed to Harm (NNH)

If patients were treated with 400 mg celecoxib daily for three months rather than naproxen (1,000 mg), 1 in every 4 or 5 patients would have an ulcer ≥ 3 mm (1 RCT) [19]

If patients were treated with 400 mg celecoxib daily for six months rather than diclofenac (150 mg), 1 in every 9 patients would have an ulcer ≥ 3 mm (1 RCT) [19]

If patients were treated with 400 mg celecoxib daily for three months rather than naproxen (1,000 mg), 1 in every 7 patients would have a UGI ulcer (3 RCTs) [21]*

It patients were treated with 400 mg celecoxib daily for three months rather than ibuprofen (2,400 mg), 1 in every 7 patients would have a UGI ulcer (1 RCT) [21]*

If patients were treated with 400 mg celecoxib daily for six months rather than diclofenac (150 mg), 1 in every 14 patients would have a UGI ulcer (1 RCT) [21]*

RCT – randomized control trial; UGI – upper gastrointestinal

* NNH values provided by the authors of the systematic review

CONCLUSION

The most prevalent disorders associated with chronic pain are OA, RA, and chronic low back pain. NSAIDs are widely used for the treatment of musculoskeletal disease because of their anti-inflammatory and analgesic effects but are associated with UGI events. Conventional or standard NSAIDs include naproxen, ibuprofen, and diclofenac. COX-2 inhibitors, a different class of NSAIDs, were developed on the premise that their use would avoid GI complications.

The COX-2 inhibitors, including celecoxib, were quickly adopted in Canada, although the cost of COX-2 inhibitors was much higher than that of non-selective NSAIDs. The efficacy, safety, cost-effectiveness, and cost-benefit ratio must be considered in the decision process. COX-2 inhibitors have been used for a relatively short period of time; therefore, practitioners need to be alert for potential side effects that are rare but serious. The challenges for clinicians and policy makers are to weigh the risks and benefits for reach patient group.

Data from reviews indicated that celecoxib was superior to placebo and had equivalent efficacy compared with non-selective NSAIDs in pain relief in patients with OA and RA for relatively short periods of time. Meanwhile, the evidence indicates that short-term use decreased GI AEs and effects compared with non-selective NSAIDs. The chronic use of celecoxib by patients with OA and RA needs further research.

The guidance document from the Canadian Consensus Conference suggests that NSAIDs (including COX-2 selective inhibitors) should be the drugs of choice for symptomatic patients with moderate to severe OA and RA. COX-2 selective inhibitors are the drug of choice for patients with risk factors for PUB. The current evidence, based on 3 to 6 months of follow-up, suggests that non-selective NSAIDs are as effective as celecoxib. The safety profile, however, is not that straightforward. Although there was a significant reduction in ulcers at 3 to 6 months follow-up for patients taking celecoxib compared with those on non-selective NSAIDs, there may be a significantly higher rate of cardiovascular events associated with celecoxib that has not yet been explored in studies with long periods (more than 6 months) of follow-up in this patient group with OA and RA.

Further investigations are required to assess possible cardiovascular risks of celecoxib and other COX-2 inhibitors. Until then, caution should be exercised in prescribing these agents to patients at risk of cardiovascular disease.

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APPENDIX A: SEARCH AND METHODOLOGY

Search

The literature search was conducted by the AHFMR Research Librarian between March 01, 2004, and March 09, 2004. The search focused only on SRs (Table A.1). Major electronic databases used included Cochrane Library, NHS Centre for Reviews and Dissemination (CRD Databases: NHSEED, HTA, DARE), PubMed, EMBASE, CINAHL, and Web of Science. In addition, relevant library collections, web sites of practice guidelines, regulatory agencies, evidence-based resources, and other HTA-related agency resources (AETMIS, CCOHTA, ECRI) were searched. Internet search engines were also used to locate grey literature. Medical subject headings (MeSH) related to the topic are cyclo-oxygenase, pain, anti-inflammatory agents, and non-steroidal and keywords are COX II, COX-2, and NSAID.

An updated search was completed on November 26, 2004 (Table A.2). The updated search included the same electronic databases and MeSH and focused only on celecoxib. The keywords included were cyclooxygenase , COX II, COX 2, NSAID*, celecoxib, celebrex, and chronic pain. The updated search was conducted to identify new SRs published since March 2004 and also RCTs on celecoxib published since the search date of the SRs (July 2002).

Rofecoxib (Vioxx®) was included in the first search strategy but SRs only referring to rofecoxib were excluded as a result of the withdrawal of this drug from the market September 30, 2004.

Also, ad-hoc information following the withdrawal of rofecoxib such as position papers, public health alerts, searches of the FDA and HC sites, and information on the safety of COX-2 inhibitors including celecoxib were retrieved and referred to in the report.

Table A.1: Databases and search terms used in the search strategy (March 2004)

Database	Platform	Searched	Search Terms
CORE DATABASES			
Cochrane Library (UK): Database of Systematic Reviews	Issue 3, 2004 Licensed Resource Update Software	March 02, 2004	#1 Cyclooxygenase inhibitors OR anti-inflammatory agents non-steroidal #2 pain OR analgesics OR analgesia OR myofascial pain syndromes #3 #1 AND #2
CRD (UK): Health Technology Assessment Database NHS Economic Evaluation Database Database of Reviews of Effects	http://nhscrd.york.ac.uk	March 02, 2004	(Cyclooxygenase-inhibitors OR COXII OR COX2) AND (pain OR analgesia OR analgesics OR myofascial pain syndromes)
PubMed National Library of Medicine (MEDLINE, Pre-MEDLINE, HealthSTAR)	http://www.pubmed.gov	March 02, 2004	#1 cyclooxygenase inhibitors OR anti-inflammatory agents, non-steroidal #2 “COX-II” OR “COX-2” OR COXII OR COX2 OR cyclooxygenase2 OR “cyclooxygenase 2” OR “cyclo oxygenase2” OR “cyclo oxygenase 2” OR cyclooxygenaseII OR cyclooxygenase2 OR “cyclo oxygenaseII” OR “cyclo oxygenase II” OR “cyclooxygenase II” #3 rofecoxib OR vioxx OR celecoxib OR celebrex OR meloxicam OR mobicox OR mobic OR etodolac OR lodine OR valdecoxib OR bextra OR lumiracoxib OR prexige OR etoricoxib OR arcoxia OR nimesulide OR methanesulfonamide #4= #2 OR #3 #5= #4 AND #1 #6 pain OR analgesics OR analgesia OR myofascial pain syndromes #7 #5 AND #6 #8 #7 AND (systematic [sb] OR review OR overview OR meta-analysis OR metaanalysis) #9 #7 AND (systematic [sb] OR review[ti] OR overview [ti] OR meta-analysis [ti] OR metaanalysis [ti]) #10 #8 OR #9 Limits: Publication date from 1997 and English language

Table A.1: Databases and search terms used in the search strategy (March 2004) (cont'd)

Database	Platform	Searched	Search Terms
CORE DATABASES (cont'd)			
ISI: Web of Science Science and Social Sciences Citation Index	Licensed Resource ISI	March 02, 2004	TS=((COXII OR COX2 OR COX II OR COX 2 OR cyclooxygenase inhibit*) AND pain AND (meta-analysis OR metaanalysis OR review OR overview OR assessment OR guideline*)) Limits: Publication date from 1998
CINAHL	Licensed Resource ISI	March 02, 2004	#1 exp Cox-2 Inhibitors/ #2 exp pelvic pain/ or exp patellofemoral pain syndrome/ or exp facial pain/ or exp "unspecified pain (SABA HHCC)"/ or exp pain/ or exp referred pain/ or exp back pain/ or exp chronic pain/ or exp "chronic pain (SABA HHCC)"/ or pain.mp. or exp muscle pain/ or exp nipple pain/ or exp low back pain/ or exp "chronic pain (NANDA)"/ or exp phantom pain/ or exp myofascial pain syndromes/ or exp abdominal pain/ or exp shoulder pain/ or exp "pain (OMAHA)"/ or exp "pain control (SABA HHCC)"/ or exp neck pain/ or exp complex regional pain syndromes/ or exp "pain (NANDA)"/ #3 (rofecoxib or vioxx).mp. [mp=title, cinahl subject headings, abstract, instrumentation] #4 (celecoxib or celebrex).mp. [mp=title, cinahl subject headings, abstract, instrumentation] #5 (meloxicam or mobicox or mobic).mp. [mp=title, cinahl subject headings, abstract, instrumentation] #6 (etodolac or lodine).mp. [mp=title, cinahl subject headings, abstract, instrumentation] #7 (valdecoxib or bextra).mp. [mp=title, cinahl subject headings, abstract, instrumentation] #8 (lumiracoxib or prexige).mp. [mp=title, cinahl subject headings, abstract, instrumentation] #9 (etoricoxib or arcoxia).mp. [mp=title, cinahl subject headings, abstract, instrumentation] #10 (nimesulide or methanesulfonamide).mp. [mp=title, cinahl subject headings, abstract, instrumentation] #11 1 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 #12 11 and 2 Limits: English language and publication date from 1998

Table A.1: Databases and search terms used in the search strategy (March 2004) (cont'd)

Database	Platform	Searched	Search Terms
CORE DATABASES (cont'd)			
EMBASE	Ovid	March 02, 2004	#1 exp cyclooxygenase 2 inhibitor/ #2 exp leg pain/ or exp pelvis pain syndrome/ or exp flank pain/ or exp stomach pain/ or phantom pain/ or exp bone pain/ or exp abdominal pain/ or pain.mp. or exp myofascial pain/ or exp visceral pain/ or exp thorax pain/ or exp shoulder pain/ or exp face pain/ or exp tooth pain/ or exp chronic pain/ or exp injection pain/ or exp low back pain/ or exp neck pain/ or exp pain/ or exp "headache and fascial pain"/ or exp complex regional pain syndrome/ or exp radicular pain/ or exp intractable pain/ or exp epigastric pain/ #3 (rofecoxib or vioxx).mp. #4 (celecoxib or celebrex).mp. #5 (meloxicam or mobicox or mobic).mp. #6 (etodolac or lodine).mp. #7 (valdecoxib or bextra).mp. #8 (lumiracoxib or prexige).mp. #9 (etoricoxib or arcoxia).mp. #10 (nimesulide or methanesulfonamide).mp. #11 meta analysis/ #12 systematic review.mp. #13 review/ #14 exp practice guideline/ #15 exp biomedical technology assessment/ or technology assessment.mp. #16 1 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 #17 16 and 2 #18 11 or 12 or 13 or 14 or 15 #19 17 and 18 Limits: Human studies only, English language, publication date from 1998

Limits: Searches were limited to publication dates: 1998–2004, where such function is available, publication type: limited to systematic reviews, where function is available; language: English only; studies: human studies only.

Notes: * is a truncation character that retrieves all possible suffix variations of the root word (surg* retrieves surgery, surgical, surgeon, etc.). In databases accessed via the Ovid platform, the truncation character is $.

Table A.2: Databases and search terms used in the updated search strategy (November 2004)

Database	Platform	Date Searched	Search Terms †*
Core Databases			
The Cochrane Library Database of Systematic Reviews	Issue 3, 2004 Licensed Resource Update Software	November 24, 2004	#1 (Cyclooxygenase inhibitors OR anti-inflammatory agents non-steroidal OR COX OR celebrex OR celecoxib) #2 (pain OR analgesics OR analgesia OR chronic pain) #3 (Arthritis OR rheumatoid arthrit* OR osteoarthrit*) #4 #1 AND #2 AND #3
CRD (UK): Health Technology Assessment Database NHS Economic Evaluation Database Database of Reviews of Effects	http://nhscrd.york.ac.uk	November 24, 2004	#1 (Cyclooxygenase inhibitor* OR COXII OR COX2 OR celecoxib OR celebrex) #2 (pain OR analges* OR chronic pain) #3 (Arthritis OR rheumatoid arthrit* OR osteoarthrit*) #4 #1 AND #2 AND #3
ISI: Web of Science Science Citation Index and Social Sciences Citation Index	Licensed Resource ISI	November 24, 2004	#1 TS=(COXII OR COX2 OR COX II OR COX 2 OR cyclooxygenase inhibit*) #2 TS= (pain or chronic pain) #3 TS=(arthrit* OR rheumatoid arthrit* OR osteoarthrit*) #4 TS=(meta-analysis OR meta analysis OR review OR overview OR assessment OR guideline* or clinical trial* OR randomised controlled trial* OR RCT OR "double blind*) #5 (#1 AND #2 AND #3 AND #4)
EMBASE	Ovid: Licensed Resource	November 24, 2004	#1(exp Cox-2 Inhibitors/ OR cyclooxygenase 2 inhibitor$/ OR COX II OR COX-2 OR COX 2 OR COX-II OR celecoxib OR celebrex) #2 (exp JUVENILE RHEUMATOID ARTHRITIS/ or exp CHRONIC ARTHRITIS/ or exp ARTHRITIS/ or exp KNEE ARTHRITIS/ or exp RHEUMATOID ARTHRITIS/ or arthritis) #3 exp chronic pain/ OR "chronic pain" #4 (#1 AND #2 AND #3) #5 Limited to systematic reviews OR meta-analyses OR RCTs (see search hedges below) #4 AND #5

Table A.2: Databases and search terms used in the updated search strategy (November 2004) (cont'd)

Database	Platform	Date Searched	Search Terms † *
Core Databases			
PubMed National Library of Medicine (MEDLINE, Pre-MEDLINE, HealthSTAR)	http://www.pubmed.gov	November 24, 2004	#1 cyclooxygenase inhibitors OR anti-inflammatory agents, non-steroidal or NSAID* #2 "COX-II" OR "COX-2" OR COXII OR COX2 OR cyclooxygenase2 OR "cyclooxygenase 2" OR "cyclo oxygenase2" OR "cyclo oxygenase 2" OR cyclooxygenaseII Orcyclooxygenase2 OR "cyclo oxygenaseII" OR "cyclo oxygenase II" OR "cyclooxygenase II" OR celecoxib* OR celebrex #3 pain OR analgesics OR analgesia OR myofascial pain syndromes #4 Arthritis/ OR (arthrit* OR osteoarthrit* OR rheumatoid arthrit*) #5 (#1 OR #2) AND #3 AND #4) #6 #5 AND systematic[sb] #7 #5 Limited to meta-analysis #8 #5 Limited to randomized controlled trial #9 review[PT] AND (medline OR pubmed) #10 meta-analysis[PT] OR Cochrane Database Syst Rev #11 (meta-analysis OR meta-anal* OR metaanal* OR quantitativ* review* OR quantitative* overview* OR systematic* review* OR systematic* overview* OR methodologic* review* OR methodologic* overview*) #12 (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh]) #13 #5 AND (#9 OR #10 OR #11 OR #12) #13 #6 OR #7 OR #8 OR #13

Table A.2: Databases and search terms used in the updated search strategy (November 2004) (cont'd)

Database	Platform	Date Searched	Search Terms [†] [*]
Core Databases			
CINAHL	Ovid: Licensed Resource	November 24, 2004	#1 exp Cox-2 Inhibitors/ OR cyclooxygenase 2 inhibitor$/ OR COX II OR COX-2 OR COX 2 OR COX-II OR celecoxib OR celebrex.mp. #2 exp *arthritis/ OR (arthrit$ OR osteoarthrit$ OR rheumatoid arthrit$) #3 exp "chronic pain (NANDA)"/ OR exp myofascial pain syndromes/ OR exp "pain (OMAHA)"/ OR exp "pain control (SABA HHCC)"/ OR exp complex regional pain syndromes/ OR exp "pain (NANDA)"/ #4 (#1 AND #2 AND #3) #5 Limited to systematic reviews OR meta-analyses OR RCTs (see search hedges below) #4 AND #5

Limits: [†] Searches were limited to publication dates: 1998–2004, where such function is available; publication type was limited to systematic reviews, randomized controlled trials, and meta-analyses; language: English only studies.

Notes: * / $ are truncation characters that retrieve all possible suffix variations of the root word (surg* / surg$ retrieves surgery, surgical, surgeon, etc.) In databases accessed via the Ovid platform, the truncation character is $.

Search Hedges: Hedges for systematic reviews, meta-analyses, and randomized controlled trials were used (where available) to limit the search results.

Search Hedges:

Systematic Reviews (EMBASE and CINAHL on Ovid Platform)
4 meta-analysis.pt.
5 (meta-anal$ or metaanal$).mp.
6 (((quantitativ$ adj3 review$1) or quantitativ$) adj3 overview$).mp.
7 (((systematic adj3 review$1) or systematic) adj3 overview$1).mp.
8 (((methodologic adj3 review$1) or methodologic) adj3 overview$).mp.
9 (integrat$ adj5 research).mp.
10 (quantitativ$ adj3 synthes$).mp.
11 or/4-10
12 review.pt. or (review$ or overview$).mp.
13 (medline or medlars or pubmed or index medicus or embase or cochrane).mp.
14 (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp.
15 (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index).mp.
16 (hand search$ or manual search$).mp.
17 ((((electronic adj3 database$) or bibliographic) adj3 database$) or periodical index$).mp.
18 (pooling or pooled or mantel haenszel).mp.
19 (peto or der simonian or dersimonian or fixed effect$).mp.
20 ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp.
21 or/13-20
22 12 and 21
23 11 or 22
24 (hta$ or health technology assessment$ or biomedical technology assessment$).mp.
25 technology assessment, biomedical/ or biomedical technology asssessment/
26 24 or 25
27 23 or 26

Meta-Analyses (EMBASE and CINAHL on Ovid Platform)
1 meta-analysis.pt.
2 (meta-anal$ or metaanal$).mp.
3 (((quantitativ$ adj3 review$1) or quantitativ$) adj3 overview$).mp.
4 (((systematic adj3 review$1) or systematic) adj3 overview$1).mp.

5 (((methodologic adj3 review$1) or methodologic) adj3 overview$).mp.
6 (integrat$ adj5 research).mp.
7 (quantitativ$ adj3 synthes$).mp.
8 or/1-7
9 review.pt. or (review$ or overview$).mp.
10 (medline or medlars or pubmed or index medicus or embase or cochrane).mp.
11 (scisearch or web of science or psycinfo or psychinfo or cinahl or cinhal).mp.
12 (excerpta medica or psychlit or psyclit or current contents or science citation index or sciences citation index).mp.
13 (hand search$ or manual search$).mp.
14 ((((electronic adj3 database$) or bibliographic) adj3 database$) or periodical index$).mp.
15 (pooling or pooled or mantel haenszel).mp.
16 (peto or der simonian or dersimonian or fixed effect$).mp.
17 ((combine$ or combining) adj5 (data or trial or trials or studies or study or result or results)).mp.
18 or/10-17
19 9 and 18
20 8 or 19
21 (hta$ or health technology assessment$ or biomedical technology assessment$).mp.
22 technology assessment, biomedical/ or biomedical technology assessment/
23 21 or 22
24 20 or 23

Randomized Controlled Trials (EMBASE and CINAHL on Ovid Platform)
1 Randomized Controlled Trial/
2 exp Randomization/
3 Double Blind Procedure/
4 Single Blind Procedure/
5 or/1-4
6 Clinical Trial/
7 (clin$ adj25 trial$).mp.
8 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.
9 exp Placebo/
10 (placebo$ or random$).mp.
11 exp Methodology/
12 exp Comparative Study/
13 exp Evaluation/ (29666)
14 exp Follow Up/ (112433)
15 exp Prospective Study/ (34498)
16 (control$ or prospectiv$ or volunteer$).mp.
17 or/6-16
18 5 or 17
19 limit 18 to human
20 Non-human/
21 19 not 20

Methodology

The studies identified by the search strategies were retrieved, reviewed, and assessed to determine the relevance of each study. Inclusion criteria were as follows:

- **Intervention**: COX-2 inhibitor drugs for the first search and only celecoxib for the updated search
- **Comparison**: non-selective NSAIDs, other COX-2 inhibitors, and/or placebo
- **Indication**: OA and/or RA
- **Target population**: all ages
- **Level of evidence**: qualitative, semi-qualitative SRs and meta-analysis with clear presentation of the RCTs included, with results presented separately for different

periods of follow-up, dosages of the intervention, and comparator drugs; RCTs published since July 2002

- **Publication limits**: starting with 1998
- **Language**: English
- **Abstract** of the study available

The exclusion criteria were as follows:

- Any other study design besides qualitative and semi-qualitative SR or meta-analysis excepting for RCTs published since July 2002
- SRs on rofecoxib (Vioxx®) alone because this COX-2 inhibitor is no longer available on the national and international marketplace
- SRs that presented results from confidential studies (RCTs) without information available in the published report
- SRs that included in the analysis RCTs with variability in the follow-up periods and/or lumped drugs based on class (group non-selective NSAIDs or COX-2 inhibitors, and different dosages)
- Studies older than 1998
- Language: other than English

The best study designs available from the first search based on the inclusion criteria are two meta-analyses that presented results on the efficacy/effectiveness of celecoxib administered to patients with RA and the safety of celecoxib administered to patients with OA and RA. The authors of both SRs did not specify if the patients in the RCTs were being treated for chronic pain. The methodological quality assessment of these SRs was conducted by one researcher using a checklist (see Appendix D). The SR by Garner et al. [19] was rated as acceptable while the Ashcroft et al. [21] review was of acceptable to poor quality.

The updated search was focused only on celecoxib. The search did not identify a recent SR but did identify five RCTs that presented results on the efficacy/effectiveness of celecoxib for the treatment of patients with OA and the safety of celecoxib for patients with RA and OA, published since July 2002. Three RCTs presented information on patients who have chronic pain, while two RCTs focused on acute pain and pain in a flare state. Because of its importance, information from CLASS is also presented, although the study was published in 2000. CLASS is the largest and longest-running RCT that reported results on GI toxicity with celecoxib versus NSAIDs administered to patients with OA and RA.

In Appendix B.1 and B.2, the results are summarized as extracted from SRs (Tables B.1.1 and B.1.2) and RCTs (Table B.2.1) on the efficacy/effectiveness and the safety of celecoxib compared with non-selective NSAIDs and/or another COX-2 inhibitor and/or placebo. In order to simplify presentation, Tables B.1.1 and B.1.2 present only statistically and/or clinically significant results (extractions were done by two researchers). Detailed information about outcomes that were found to be SS or not SS is presented in the report (see sections titled "Evidence from SRs" and "Evidence from RCTs").

For the safety analysis, an explanation of the data included in the tables is as follows:

- Relative Risk (RR) and its confidence interval (CI). A value lower than 1 shows that the experimental treatment (COX-2 selective inhibitor) is safer than the control and if the CI does not include 1, than statistical significance is assumed. It should be noted that an SS result may not be clinically significant. RR = experimental event rate (EER)/control event rate (CER)
- Absolute Risk Reduction (ARR) and its CI. If the AEs occur more often in the control group than in the treatment groups, this suggests that the intervention is beneficial. ARR= CER – EER
- Number Needed to Harm (NNH). Used to measure AEs. Provides information on the number of patients that need to be treated in order to obtain an event (in this case an AE). Larger values are important because they indicate fewer AEs. NNH= 1/ARR = 1/CER-EER

  The ARR and NNH values were calculated [19] or provided by the authors of the review [21]. The NNH was calculated for comparable groups in terms of comparators (non-selective NSAIDs, placebo), follow-up period, and treatment doses.

The SRs and RCTs that did not meet our inclusion criteria are presented in Appendix E[28]. Three SRs [24 54] were not excluded because of their methodological quality, but because relevant clinical information was not presented as required by our inclusion criteria. In these SRs, results were pooled from studies with different periods of follow-up, daily dosages, interventions, and/or comparators.

Analysis and synthesis of the results were conducted by two researchers.

Outcome measures

Table A.3: Efficacy/effectiveness outcome measures

Study	Outcome Measures for OA and RA
Garner et al. [19] **SR**	**RA** Outcome Measures for Arthritis Clinical Trials (OMERACT): Number of tender joints per patient Number of swollen joints per patient Patient's assessment of pain Patient's and physician's global assessments of disease activity Patient's assessment of physical function Laboratory evaluation of one acute-phase reactant Radiological damage The American College of Rheumatology responder index (ACR-20) Health Assessment Questionnaire (HAQ) functional disability index
Bianchi and Broggini [29] **RCT**	**OA** Pain intensity (VAS at baseline, 0.25, 0.5, 1, 2, 3, and 12 hours) Analgesic efficacy Total pain relief over 3 hours (TOPAR 3) Patient's assessment of pain Total number of rescue medications used (paracetamol tablets)
Hawel et al. [30] **RCT**	**OA** Western Ontario and McMaster Universities osteoarthritis index (WOMAC OA index) Intensity of pain at night, at rest, start pain, pain at movement Handicap Restriction of movement Quality of life Physician's and patient's subjective assessment of global efficacy Patient's subjective global assessment of response to therapy (PGART)
Pincus et al. [31] **2 RCTs**	**OA** WOMAC OA index VAS to assess pain, stiffness, function General and specific to affected joint Multidimensional Health Assessment Questionnaire (MDHAQ) VAS to assess pain and global status Short Form-36 (SF-36) health survey Patient preferences for treatment

Table A.3: Efficacy/effectiveness outcome measures (cont'd)

Study	Outcome Measures for OA and RA
Gibofsky et al. [32] **RCT**	**OA** Primary measures: Patient's assessment of arthritis pain on the VAS (OA pain) at week 6 WOMAC OA index at week 6 Secondary measures: Patient's and physician's global assessments Patient's assessment of arthritis pain on the VAS (pain on walking) Patient's assessment of arthritis pain on the WOMAC subscales for pain, stiffness, and physical function.

OA – osteoarthritis; RA – rheumatoid arthritis; RCT – randomized control trial; SR – systematic review; VAS – Visual Analogue Scale

Table A.4: Safety outcome measures

Study	Outcome Measures for OA and RA
Garner et al. [19] **SR**	**RA** Incidence and severity of: Total withdrawals; withdrawals due to AEs, gastrointestinal AEs, lack of efficacy Total AEs associated with therapy: edema, hypertension Number of patients with cardiovascular event(s) Number of patients presenting clinically with perforations and/or ulcer and/or bleed Number of patients with erosions or ulcers detected by endoscopy Deaths
Ashcroft et al. [21] **SR**	**OA and RA** Incidence of endoscopic gastroduodenal ulcers
Goldstein et al. [17] **RCT**	**OA and RA** Severity of Dyspepsia Assessment (SODA) questionnaire Pain intensity Non-pain symptoms Satisfaction with dyspepsia-related health
Bianchi and Broggini [29] **RCT**	Overall tolerability of the treatment (5-point categorical scale)

Table A.4: Safety outcome measures (cont'd)

Study	Outcome Measures for OA and RA
Hawel et al. [30] **RCT**	**OA** Withdraw due to adverse drug reactions Incidence of adverse drug reactions Gastrointestinal complaints Central nervous system complaints Skin Cardiovascular Physician's and patient's subjective assessment of global tolerability
Pincus et al. [31] **RCT**	**OA** Number of patients with any adverse effect Number of patients with serious effects Number of patients with any gastrointestinal effect (diarrhea, dyspepsia, nausea, flatulence) Number of patients with respiratory tract infection Number of patients with headache
Gibofsky et al. [32] **RCT**	**OA** Number of patients with any adverse effect Number of adverse effects causing withdrawal Number of patients with different adverse effects General symptoms: headache, respiratory infections and rhinitis, leg cramps, accidental injury Gastrointestinal symptoms: dyspepsia, diarrhea, abdominal pain Cardiovascular events: hypertension

AE – adverse event; OA – osteoarthritis; RA – rheumatoid arthritis; RCT – randomized control trial; SR – systematic review

APPENDIX B.1: SYSTEMATIC REVIEWS ON EFFICACY/EFFECTIVENESS AND SAFETY

Table B.1.1: Efficacy/effectiveness of celecoxib for the treatment of RA*

Study	Comparator dose/day, # RCTs	Celecoxib dose/day	Follow-up (weeks)	Results
Garner et al. [19] 2002 Systematic review	Placebo (2 RCTs) N = 316 [85 (4w)+231(12w)]	80 mg, 200 mg, 400 mg, 800 mg N = 1,023	4, 12	In the RCT (12 weeks), celecoxib produced significant improvement for all measures of efficacy compared with the placebo group. There was no dose response found. The ACR-20 response was higher for celecoxib compared with placebo; celecoxib 400-mg and 800-mg doses were significantly different from placebo as assessed by patients' and physicians' global assessment, as well as the reduction in the number of tender and painful joints. In the other RCT (4 weeks), the withdrawals due to lack of efficacy were lower for all active treatment groups compared with placebo. The improvement produced with celecoxib was SS according to ACR 20 criteria in the 400-mg and 800-mg daily groups. The difference between the 80-mg group and placebo was only SS in the first week. The mean change in the patients' global assessment was SS for patients taking celecoxib 400 and 800 mg daily than for those taking placebo at all time points ($P \leq 0.001$).
	Naproxen (1 RCT) 1,000 mg N = 225	200 mg, 400 mg, 800 mg N = 693	12	The only SS difference was that individuals taking 400 mg celecoxib daily showed greater improvement measured by patient and physician global assessment and those taking 800 mg showed greater improvement on the HAQ functional disability score.
	Diclofenac (1 RCT) 150 mg N = 329	400 mg N = 326	24	There were no differences in the number of painful or swollen joints, pain and inflammation, HAQ assessments, C-reactive protein, and patient or physician global assessments.

ACR-20 – American College of Rheumatology responder index; HAQ – Health Assessment Questionnaire index; OA – osteoarthritis; RA – rheumatoid arthritis; RCT – randomized control trial; SS – statistically significant

***** Only SS or clinically significant values (scores, relative risks, and confidence intervals) are presented in order to simplify the presentation. Detailed information about all results (SS or not SS) is presented in text.

Table B.1.2: Safety of celecoxib for the treatment of OA and RA*

Garner et al. [19], RA						
Results	**Comparator** Dose/day	**Celecoxib** Dose/day	**Follow-up** (weeks)	**RR, 95% CI**	**ARR %, CI**	**NNH**
Total AEs	**Placebo** (1 RCT) (128/231)	200 mg (164/240)	12	1.23 (1.07, 1.42)	12.9 (4.2, 21.6)	8
Withdrawal GI	**Naproxen** (1 RCT) 1,000 mg (11/225)	200 mg (3/240)	12	0.26 (0.07, 0.90)	3.6 (0.5, 6.8)	-
Ulcer ≥ 3mm (endoscope)	---//--- (1 RCT) (36/137)	---//--- (9/148)	12	0.23 (0.12, 0.46)	20.2 (11.9, 20.5)	5
	---//--- (2 RCTs) (53/196)	400 mg 11/202	12	0.20 (0.11, 0.38)	21.6 (14.6, 28.6)	5
	---//--- (1 RCT) (36/137)	800 mg (8/130)	12	0.23 (0.11, 0.48)	20.2 (11.7, 28.6)	5
Total GI AEs	**Diclofenac** (1 RCT) 150 mg (159/329)	400 mg (118/326)	24	0.75 (0.62-0.90)	12.13 (4.6, 19.7)	9
Withdrawal GI	---//--- (51/329)	---//--- (18/326)	24	0.36 (0.21, 0.60)	9.98 (5.4-, 14.6)	-
Withdrawal AE	---//--- (64/329)	---//--- (34/326)	24	0.54 (0.36, 0.79)	9.02 (3.6, 14.4)	-
Ulcer ≥3 mm (endoscoped)	---//--- (33/218)	---//--- (8/212)	24	0.25 (0.12, 0.53)	11.36 (6.0, 16.8)	9
Gastric erosion, ulcers, or both	---//--- (74/218)	---//--- (38/212)	24	0.53 (0.37, 0.74)	16.02 (7.9, 24.2)	7
Duodenal erosion, ulcers, or both	---//--- (23/218)	---//--- (11/212)	24	0.49 (0.25, 0.98)	5.36 (0.3, 10.4)	19

Table B.1.2: Safety of celecoxib for the treatment of OA and RA (cont'd)*

Garner et al. [19] OA and RA						
Results	**Comparator** Dose/day	**Celecoxib** Dose/day	**Follow-up** (weeks)	**RR, 95% CI**	**ARR %, CI**	**NNH**
Ulcer ≥ 3 mm (endoscope)	**Naproxen** (1 RCT) 1,000 mg (87/214)	400 mg (18/211)	12	0.21 (0.13, 0.34)	32.12 (24.5, 39.7)	4

Table B.1.2: Safety of celecoxib for the treatment of OA and RA (cont'd)*

Ashcroft et al. [21], 2001 OA and RA						
Results	**Comparator** Dose/day	**Celecoxib** dose/day	**Follow-up** (weeks)	**RR, CI**	**ARR %, CI**	**NNH#**
Upper ulcer rates (endoscope)	**Placebo** (2 RCTs) (N = 473)	400 mg (N = 468)	12	2.35 (1.20 5.38)	0.02 (-0.001 0.04)	-
	Naproxen (1 RCT) 1,000 mg (N = 226)	100 mg (N = 252)	12	0.21 (0.10 0.45)	-0.12 (-0.17 -0.07)	-
	---//--- (2 RCTs) (N = 451)	200 mg (N = 480)	12	0.22 (0.13 0.37)	-0.12 (-0.16 -0.08)	9
	---//--- (3 RCTs) (N = 718)	400 mg (N = 738)	12	0.24 (0.17 0.33)	-0.16 (-0.25 -0.07)	7
	---//--- (1 RCT) (N = 225)	800 mg (N = 218)	12	0.23 (0.11 0.48)	-0.12 (-0.18 -0.07)	-
	Diclofenac (1 RCT)§ 150 mg (N = 329)	400 mg (N = 326)	24	0.24 (0.11 0.52)	-0.08 (-0.11 -0.04)	14
	Ibuprofen (1 RCT) 2,400 mg (N = 346)	400 mg (N = 365)	12	0.30 (0.20 0.46)	-0.16 (-0.21 -0.11)	7

AE – adverse event; ARR – absolute risk reduction; CI – confidence interval; GI – gastrointestinal; NNH – number needed to harm; OA – osteoarthritis; RA – rheumatoid arthritis; RCT – randomized control trial; RR – relative risk; SS – statistically significant

***** Only SS or clinically significant values are presented in order to simplify the presentation. Detailed information about all results (SS or not SS) is presented in text.

#NNH was calculated by the authors.

§A study with a follow-up of 12 weeks was not SS; RR = 0.73 (0.45 1.20).

APPENDIX B.2: RCTS ON EFFICACY/EFFECTIVENESS AND SAFETY*

Table B.2.1: Efficacy/effectiveness and safety of celecoxib for the treatment of OA and RA

Study **Condition**	**Comparator** dose/day	**Celecoxib** dose/day	**Follow-up**	**Results**
Goldstein et al.[17] 2002 RCT OA and RA	Diclofenac 150 mg N = 1816	800 mg daily N = 1791	4, 13, 26, 39, and 52 weeks, and early termination	**Efficacy/effectiveness** Not assessed **Safety** Results from the Deverity of Dyspepsia Assessment (SODA) questionnaire: Pain intensity: changes higher (indicating a worsening status) for diclofenac (SS) compared with celecoxib at each follow-up assessment ($p < 0.001$). Non-pain symptoms scores: celecoxib was better than diclofenac (SS) at 4 weeks ($p = 0.005$), but not at weeks 13, 26, and 52 ($p = 0.12$ and $p > 0.20$) Satisfaction with Dyspepsia-Related Health Scale (celecoxib was superior to diclofenac [SS] at each follow-up assessment ($p<0.001$) Patients treated with celecoxib 800 mg daily had a lower overall incidence of any gastrointestinal adverse events (40.4% versus 48.1%; $p < 0.001$). Celecoxib had lower rates for each gastrointestinal adverse event (dyspepsia, abdominal pain, diarrhea, nausea, constipation, flatulence). 12% of diclofenac-treated patients withdrew due to a gastrointestinal adverse event, compared with 8.9% of celecoxib-treated patients ($p < 0.001$)

Table B.2.1: Efficacy/effectiveness and safety of celecoxib for the treatment of OA and RA (cont'd)

Study Condition	Comparator dose/day	Celecoxib dose/day	Follow-up	Results
Bianchi and Broggini [29] 2003 Cross-over RCT OA of the knee	Nimesulide (Aulin®) 100 mg daily N = 31 Rofecoxib (Vioxx®)* 25 mg daily N = 31 * Vioxx was withdrawn from the market in September 2004	200 mg daily N = 31	3 weeks (1 week each treatment)	**Efficacy/effectiveness** The overall analgesic effect over the first 3 hours, as measured by TOPAR 3, was more marked (SS) for a single dose of nimesulide 100 mg than for a single dose of celecoxib 200 mg or rofecoxib 25 mg ($p < 0.05$). The analgesic efficacy of nimesulide measured in day 7 was also superior to that of the other two drugs ($p < 0.05$). Patient baseline pain assessment in the first day, as well as in the seventh day of the treatment, was similar for all treatment groups, with no SS difference in the VAS scores obtained in the three groups of patients. **Safety** Not assessed
Hawel et al. [30] 2003 RCT OA of the hip	Dexibuprofen 800 mg daily N = 74	200 mg daily N = 74	15 days	**Efficacy/effectiveness** The WOMAC OA index during the 15-day treatment period (primary efficacy criterion) and the WOMAC OA index on day 8, pain at night, pain at rest, start pain, pain at movement, handicap, restriction of movement, and quality of life (secondary efficacy criteria) improved with both drugs (dexibuprofen and celecoxib). Differences were not SS. There were no SS differences in the judgement of the efficacy by physicians and patients and the PGART on day 15, between both treatment groups. **Safety** The overall incidence of AEs was 12.16% (9 patients) in the dexibuprofen group (gastrointestinal complaints, 6 patients; central nervous system complaints, 2 patients; skin reaction, 1 patient) and 13.51% (10 patients) in the celecoxib group (gastrointestinal complaints, 7 patients; skin, 1 patient; cardiovascular, 1 patient; other, 1 patient). One patient in the celecoxib group had two different adverse drug reactions. Statistical significance was not measured.

Table B.2.1: Efficacy/effectiveness and safety of celecoxib for the treatment of OA and RA (cont'd)

Study Condition	**Comparator** dose/day	**Celecoxib** dose/day	**Follow-up**	**Results**
Pincus et al. [31] 2004 2 cross-over RCTs OA of the knee and hip PACES-a Period I, N = 524 Period II, N = 382 PACES-b (I+II) Period I, N = 556 Period II, N = 416	Acetaminophen (paracetamol) 1,000 mg four times a day PACES-a: Period I, n = 171 Period II, n = 125 PACES-b: Period I, n = 185 Period II, n = 145 Placebo PACES-a: Period I, n = 172 Period II, n = 91 PACES-b: Period I, n = 182 Period II, n = 88	200 mg daily PACES-a: Period I, n = 181 Period II, n = 166 PACES-b: Period I, n = 189 Period II, n = 183	14 weeks	**Efficacy/effectiveness** Celecoxib 200 mg daily was superior to acetaminophen (SS) and acetaminophen was more efficacious than placebo (SS) in both periods of the studies with the exception of Period I of PACES-a when no SS differences between celecoxib and acetaminophen and between acetaminophen and placebo was shown, while the differences between celecoxib and placebo were significant for the WOMAC and pain VAS scores. Patient preference: celecoxib vs. acetaminophen: 53% vs. 24% in PACES-a ($p < 0.001$) 50% vs. 32% in PACES-b ($p = 0.009$) acetaminophen vs. placebo: 37% vs. 28% in PACES-a ($p = 0.340$) 48% vs. 24% in PACES-b ($p = 0.007$) **Safety** The rate of AEs was low and similar (with no SS differences) for celecoxib, acetaminophen, and placebo groups. There was no SS difference between treatment drugs for any gastrointestinal event (diarrhea, dyspepsia, nausea, flatulence), as well as for upper respiratory infection and headache, for both periods combined in PACES clinical trials. In PACES-a, eight AEs were classified as serious and required admission to hospital. Only two events, one involving an intestinal obstruction (celecoxib group) and the other increased liver enzymes (placebo group), were regarded by the investigators as potentially related to the study drug. In PACES-b, four AEs were classified as serious and required admission to hospital. All events were considered unrelated to the study drug by the investigators.

Table B.2.1: Efficacy/effectiveness and safety of celecoxib for the treatment of OA and RA (cont'd)

Study Condition	**Comparator** dose/day	**Celecoxib** dose/day	**Follow-up**	**Results**
Gibofsky et al. [32] 2003 RCT OA of the knee	Rofecoxib 25 mg daily N = 190 Placebo N = 96 * Vioxx was withdrawn from the market in September 2004	200 mg daily N = 189	6 weeks	**Efficacy/effectiveness** The pain on walking (VAS) score, WOMAC subscales pain, stiffness, physical functioning, and patient's and physician's global assessment were improved in the celecoxib group compared with placebo at week 6 ($p \leq 0.016$). There was no SS difference between the active treatments (celecoxib and rofecoxib). **Safety** The most common adverse effects in the celecoxib group were headache, 15 patients; dyspepsia, 11 patients; diarrhea, 8 patients; peripheral edema and rhinitis, 5 patients each; abdominal pain and sinusitis, 3 patients each; accidental injury and upper respiratory tract infection, 2 patients each; dizziness and hypertension, 1 patient each. In the celecoxib groups, 60% of the adverse effects were considered mild and 34% were of moderate severity. In the placebo group, 52% of the adverse effects were mild and 38% were of moderate severity.

AE – adverse event; OA – osteoarthritis; PGART – patient's global assessment of response to therapy; RA – rheumatoid arthritis; RCT – randomized control trial; SS – statistically significant; TOPAR 3 – total pain relief over three hours; VAS – Visual Analogue Scale; WOMAN OA – Western Ontario and McMaster Universities

* RCTs published since July 2002

APPENDIX C: STUDIES (RCTS) ON CELECOXIB FOR OA AND RA INCLUDED IN THE SYSTEMATIC REVIEWS

Table C.1: Studies (RCTs) on celecoxib for OA and RA included in the systematic reviews

Study, Year of Publication	Follow-up (weeks)	Garner et al. [19] 2002	Ashcroft et al. [21] 2001	Rostom et al. (CCOHTA) [24] 2003	NICE [54] 2000	Deeks et al. [28] 2002
Celecoxib RA						
Simon 1998	4	(E, S)			(?)	
Simon 1999 (Geis 1998, Zhao 2000, Study 022)	12	(E, S)	(S)	(S)	(?)	(E, S)
Emery 1999 (Geis 1998, Study 041)	24	(E, S)	(S)	(S)	(?)	(E)
Goldstein 2001	12	(E, S)		(S)		
Zhao 2000	12					(E, S)
Searle 023, 1998 (confidential)	?				(?)	
Celecoxib OA						
Bensen 1999 (FDA 021, 1998)	12		(S)	(S)	(?)	(E, S)
Study 054, 1997	12				(?)	(E, S)
Zhao 1999	12					(E, S)
SUCCESS-1 Abstract	6, 12			(S)		
McKenna 2001	2, 6			(S)		
Williams 2000	2, 6			(S)	(?)	
Searle 047, 1997 (confidential)	?				(?)	

Table C.1: Studies (RCTs) on celecoxib for OA and RA included in the systematic reviews (cont'd)

Study, Year of Publication	Follow-up	Garner et al. [19] 2002	Ashcroft et al. [21] 2001	Rostom et al. (CCOHTA) [24] 2003	NICE [54] 2000	Deeks et al. [28] 2002
Celecoxib OA (cont'd)						
Geis 1999; Searle 087	12				(?)	
Searle 118, 2000	6				(?)	
Searle 042, 1998	6				(?)	
Celecoxib RA and OA						
Silverstein 2000 CLASS (study 35/102)	26–52	(S) (mentioned)	(S) (mentioned)	(S)	(S)	(24 weeks) (S)
FDA 1998, 062	12		(S)		(?)	(S)
FDA 1998, 071	12		(S)	(S)	(?)	(S)
Goldstein 2000	2–24			(S)		

CCOHTA – Canadian Coordinating Office for Health Technology Assessment; FDA – Food and Drug Administration; OA – osteoarthritis; NICE – National Institute for Clinical Excellence; RA – rheumatoid arthritis; E – assessment of the efficacy; S – assessment of the safety.

Reviews included:
Garner et al. [19] – included in the review RCTs published up to August 2002
Ashcroft D.M. et al [21] – included in the review RCTs published and unpublished up to July 2000

Reviews excluded:
Rostom A et al. (CCOHTA) [24] – included in the review RCTs published up to May 2002
NICE Appraisal Team [54] – included in the review RCTs published and unpublished (confidential) up to July 2000
Deeks J.J. et al. [28] – included in the review RCTs published and unpublished up to May 2000

Characteristics of the SRs included [19, 21]

- Different number of published and unpublished RCTs included
- Different number of patients included
- Different periods of follow-up (4 to 24 weeks with 12 weeks of follow-up in the majority of reviews)
- Different comparator drugs: non-selective NSAIDs (naproxen, diclofenac, ibuprofen) and/or placebo and different doses of the selective NSAID, celecoxib
- Focus on the efficacy/effectiveness and/or safety of celecoxib compared with non-selective NSAIDs and/or placebo
- Access to other drugs such as aspirin, paracetamol, or corticosteroid therapy during the period of follow-up that may interfere with the intervention and comparator drugs
- Different end-points investigated: AEs such as endoscopic gastroduodenal ulcer, ulcer complications (PUB; perforations, obstruction, and bleeding), withdrawals due to AEs or GI AEs
- Failure to report other serious AEs that may be associated with the administration of selective and non-selective NSAIDs such as cardiovascular and renal problems
- The CLASS trial, the largest and longest follow-up trial that compared celecoxib to non-selective NSAIDs, was mentioned in both reviews. However, the study was not included in the meta-analyses.

Characteristics of the RCTs included [17, 29-32]

- Different number of patients included
- Different characteristics of the patients (age, ethnicity, conditions treated)
- Different comparators (selective NSAIDs, non-selective NSAIDs, acetaminophen, placebo)
- Focus on the efficacy/effectiveness and/or safety of celecoxib compared with selective NSAIDs, non-selective NSAIDs, acetaminophen, placebo
- Access to other drugs such as aspirin, paracetamol, antacids, acetaminophen, propoxyphene, or codeine during the period of follow-up
- Different periods of follow-up (range from two weeks to one year)

- Different end-points investigated mainly adverse effects (GI symptoms, general symptoms)
- Failure to report other serious AEs that may be associated with the administration of selective and non-selective NSAIDs such as cardiovascular and renal problems

APPENDIX D: QUALITY ASSESSMENT CHECKLIST FOR SYSTEMATIC REVIEWS [66-69]

Study Question

The objective(s) of the review should be stated in the abstract, introduction, or methods section.

Inclusion/Exclusion Criteria

Details of the participants, interventions, outcome measures, and types of studies considered for analysis should be stated in the abstract, introduction, or methods section of the review. If the first mention of any of these elements occurs in the results section, the review should be scored as 'not reported'. All of these elements are considered **mandatory for a quality review**, so if a review scored as 'not reported' for any of these elements, the review was not assessed further.

Search Strategy

Electronic databases

Any electronic databases used in the literature search should be listed. A review that used both Medline (or PubMed) and Embase is scored 'yes' in the quality subsection.

Other sources

Any resources or methods used in the literature search other than searching of electronic databases should be listed (e.g., pearling, hand searching of journals).

Data Extraction

Standardized method

If the data categories extracted were listed or the use of a standardized data extraction form was mentioned, then the review scores 'yes'.

Independent data extraction

If data were extracted by at least two independent reviewers, the review should be scored 'yes'. In cases where data were extracted by one reviewer and checked by another, the study scores 'no'.

Quality Assessment

Independent quality assessment

If the quality of the included studies was assessed by at least two independent reviewers, the review should be scored 'yes'. In cases where the studies were assessed by one reviewer and checked by another, the study scores 'no'.

Inter-rater agreement

Inter-rater agreement was considered to be reported either if there was a statement of the degree of difference/equivalence between the reviewers or if a statistical measure of inter-rater agreement was provided.

Data Analysis/Synthesis

Qualitative review

A qualitative review is defined as a narrative summary of the study results with no statistical analysis or pooling of results. Reviews that analyzed or discussed the results of the included studies in terms of their quality scored 'yes' in the quality subsection.

Semi-quantitative review

A semi-quantitative review incorporates a statistical analysis of individual studies without pooling the results (e.g., relative risks calculated for individual study outcomes) and/or pooling of results using only descriptive statistics (e.g., median, mean, mode, frequency). A range or confidence interval must be reported for the review to score 'yes' in the quality subsection.

Meta-analysis

This is defined as any analysis where a pooled effect estimate is calculated for at least two studies. Confidence intervals must be reported for the review to score 'yes' in the first quality subsection; results of a statistical analysis of study heterogeneity must be reported for the review to score 'yes' in the second quality subsection.

Conclusions

Clinical application of results

The clinical application of results was considered to be reported if all of the following four elements were present in the concluding section or statement of the review: treatment, treatment effect, patient group, and comparator. If only three of the four elements were present, the study was scored as 'partially reported'. A review was scored as 'not reported' if fewer than three of these elements were present.

Conclusions supported by results

The review was scored as 'yes' if the conclusions drawn by the authors of the review were supported by the evidence presented in the results section.

Conflict/Funding

A statement of conflict of interest (if any) and any funding sources should be present.

Table D.1: Critical appraisal of reviews

Review Characteristic		Garner et al. [19] 2002	Ashcroft et al [21] 2001
Study question formulated		●	●
Inclusion/ exclusion criteria	Participants	●	●
	Interventions	●	●
	Comparators	●	●
	Outcome measures	●	●
	Study type/design	●	●
Search strategy	Electronic databases	●	●
	At least Medline and Embase	✓	✓
	Other sources	●	●
Data extraction	Data extraction method	●	○
	Standardized method	✓	**X**
	Independent data extraction by at least two reviewers	✓	**X**
Quality assessment	Criteria used to assess the validity of included studies	●	○
	Independent quality assessment by at least two reviewers	✓	✓
	Inter-rater agreement for quality assessment	○	○

Table D.1: Critical appraisal of reviews (cont'd)

	Review Characteristic	Garner et al. [19], 2002	Ashcroft et al [21], 2001
Data analysis/ synthesis	Qualitative review	N/A	N/A
	Study quality used in analysis or discussion of study results		
	Semi-quantitative review	●	N/A
	Confidence interval or range reported	✓	
	Meta-analysis	N/A	●
	Precision of the results reported		✓
	Test of homogeneity conducted		✓
	Test for publication bias	○	○
Conclusions	Potential methodological limitations	○	○
	Clinical application of results	●	●
	Conclusions supported by results	✓	✓
Conflict/ funding	Conflict of interest (if any)	●	○
	Source of funding	●	○

Key for quality of reporting: Reported: ●; Partially reported: ◐; Not reported: ○; Not applicable: N/A

KEY FOR QUALITY OF REVIEW (GREY SECTIONS OF TABLE): YES = ✓; NO = X; UNCLEAR = ?

APPENDIX E: EXCLUDED SYSTEMATIC REVIEWS AND RANDOMIZED CONTROLLED STUDIES

Table E.1: Excluded systematic reviews

Author	Type of study Condition	Comments (reasons for exclusion)
Deeks et al. [28]	Meta-analysis OA, RA	Compared results with celecoxib and non-selective NSAIDs combined (naproxen, diclofenac, ibuprofen)
Lee et al. [70]	Meta-analysis OA	Compared acetaminophen with non-selective and selective NSAIDs. Pooled non-selective and selective (celecoxib, rofecoxib) NSAIDs
NICE [54]	Meta-analysis, OA, RA	Pooled results from studies with different periods of follow-up for the analysis of safety did not provide detailed information (values) on the efficacy and present results from confidential studies without providing the information
Rostom et al. (CCOHTA) [24]	Meta-analysis OA, RA	Pooled results from studies with different periods of follow-up
Schoenfeld [71]	Meta-analysis OA, RA, lumbago	Included RCTs with different periods of follow-up
Tomita et al. [72]	Semi-quantitative review RA	Pooled different non-selective and selective (meloxicam, etodolac) NSAIDs
Towheed et al. [73] (Cochrane group)	Meta-analysis OA	Assessed the efficacy and safety of acetaminophen versus placebo, versus NSAIDs (including celecoxib, rofecoxib, naproxen, ibuprofen)
Uemura et al. [74]	Semi-quantitative review OA	Presented results with NSAIDs (non-selective and selective: meloxicam, etodolac) analyzed together
Watson et al. [75] (Cochrane group)	Meta-analysis OA	Old study (the most recent substantive amendment was in November 1996). Included RCTs on etodolac as well as non-selective NSAIDs
Wegman et al. [76]	Meta-analysis OA	Compared acetaminophen with non-selective NSAIDs. COX-2 inhibitors were not included in the review.

CCOHTA – Canadian Coordinating Office for Health Technology Assessment; COX-2 – cyclo-oxygenase 2; OA – osteoarthritis; NICE – National Institute for Clinical Excellence; NSAID – non-steroidal anti-inflammatory drug; RA – rheumatoid arthritis; RCT – randomized control trial

Table E.2: Excluded randomized controlled studies

Author	Condition	Comments (reasons for exclusion)
Chan et al. [16]	Arthritis	Included patients with OA, RA, other forms of arthritis and pooled results for all conditions
Lee et al. [15]	Arthritis	Included patients with OA, RA, other forms of arthritis and pooled results for all conditions
Stengaard-Petersen et al. [77]	OA of the knee and hip	Compared satisfaction of patients with celecoxib administered in different doses and different times at which each intervention was applied. No comparison with a non-selective NSAID and/or placebo
Whelton et al. [78]	OA and systemic hypertension	Compared results obtained with celecoxib versus rofecoxib

OA – osteoarthritis; NSAID – non-steroidal anti-inflammatory drug; RA – rheumatoid arthriti