Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Celecoxib

Proprietary Product Name: Celebrex

Sponsor: Pfizer Australia Pty Ltd

August 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	23 June 2010
Active ingredient(s):	Celecoxib
Product Name(s):	Celebrex
Sponsor's Name and Address:	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
Dose form(s):	Capsules
Strength(s):	100 mg, 200 mg and 400 mg
Container(s):	Blister pack
Pack size(s):	All presentations: packs of 10, 20, 50 and 60 200 mg, 400 mg: packs of 30, 120 400mg; packs of 5
Approved Therapeutic use:	For the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. For the treatment of primary dysmenorrhoea in adults. Short-term treatment of acute pain in adults following surgery or musculoskeletal and/or soft tissue injury.
Route(s) of administration:	Oral
Dosage:	Depends on the indication but the recommended dose for most indications is 200 mg daily
ARTG Number (s)	67901, 67902 and 101341

Product Background

Celecoxib is a cyclooxygenase-2 (COX-2) inhibitor. The mechanism of action for celecoxib is attributed to inhibition of prostaglandin synthesis via inhibition of COX-2. COX-2 is induced by inflammatory stimuli, leading to the synthesis of prostaglandins, which mediate inflammation, oedema and pain. In animal models, celecoxib acts as an anti-inflammatory, antipyretic and analgesic by blocking prostaglandin synthesis via COX-2 inhibition. At therapeutic concentrations in humans, celecoxib does not inhibit COX-1.

Celecoxib was first approved in Australia in 1999 (trade name Celebrex) for the symptomatic treatment of osteoarthritis (OA) and rheumatoid arthritis (RA). It was subsequently approved for treatment of primary dysmenorrhoea (2002, trade name Celebrex), ankylosing spondylitis (AS, 2008, trade name Celebrex) and to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis, as an adjunct to surgery (FAP, 2005, trade name Onsenal). However, Pfizer does not currently distribute Onsenal in Australia. The sponsor previously submitted two applications to the TGA for the indications of acute pain (2001) and

pain post-dental surgery (1998) and these applications were unsuccessful due to insufficient evidence to support efficacy.

The sponsor has applied for an extension of indications to the registration of the selective COX-2 inhibitor Celebrex (celecoxib) to include:

Short-term treatment of acute pain in adults following surgery or musculoskeletal and/or soft tissue injury.

The sponsor considers previous objections to registration have been addressed with this hybrid literature-based submission.

There are 3 selective COX-2 inhibitors that have/had indications for management of pain in Australia:

- valdecoxib (Valdyne) was withdrawn from the Australian Register of Therapeutic Goods in 2004;
- etoricoxib (Arcoxia) is currently registered with the indication:

Treatment of acute pain, including that related to primary dysmenorrhoea and minor dental procedures. The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risk

- parecoxib (Dynastat) is registered for

A single peri-operative dose for the management of post-operative pain.

The current indications for celecoxib are:

Symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis; and treatment of primary dysmenorrhoea in adults. The usual recommended daily dose for osteoarthritis, ankylosing spondylitis and rheumatoid arthritis is 200 mg daily. For patients with rheumatoid arthritis a dose of up to 400 mg daily may be used for short-term management of disease flares or exacerbations.

For primary dysmenorrhoea the recommended dose is a single 400 mg dose then 200 mg daily. Patients may be instructed to take an additional dose of 200 mg on any given day, if needed. The maximum recommended treatment duration is five days.

Regulatory Status

In addition to indications in OA, RA, AS and FAP, celecoxib was approved for the short term management of acute pain in the USA, Canada and New Zealand in 2001, 2004 and 1999 respectively. The acute pain indication in the USA is as follows:

For the management of acute pain in adults

In New Zealand the acute pain indication is as follows:

For the management of acute pain

In Canada the acute pain indication more closely follows the proposed indication for Australia but specifies use for dental extraction, post-operative orthopaedic surgery and sprains as follows:

Celebrex (celecoxib) is also indicated for the short-term (≤ 7 days) management of moderate to severe acute pain in adults in conditions such as the following:

- *musculoskeletal and/or soft tissue trauma including sprains,*
- *post-operative orthopaedic, and*

- *pain following dental extraction.*

The maximum duration of treatment for the acute pain indication in Canada is 7 days compared with the 10 days proposed in this submission. No maximum duration is specified in the US PI. The dose recommendation in the US is the same as proposed in this submission. Celecoxib is currently approved in the European Union (EU) with indications for OA, RA, AS and FAP.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There is no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There is no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Introduction

The submission included the following studies:

1. One study related to pain following surgery:

2. Nine studies related to pain following musculoskeletal and/or soft tissue injury including six in ankle sprain, two in shoulder pain and one in low back pain.

There was also reference to the previously submitted Study 078 in 2001 for treatment of low back pain.

In addition, there was a literature review to support the submission.

Pharmacokinetics

There were no new data submitted.

Pharmacodynamics

There were no new data submitted.

Efficacy

Previously submitted efficacy data for acute pain consisted of 17 studies. Fifteen of the trials addressed the first proposed indication, the treatment of acute pain in adults. These consisted of five trials conducted in patients who had undergone dental surgery, nine trials in patients who had undergone orthopaedic or general surgery, and one trial in patients with acute non-surgical pain. Two trials in patients with dysmenorrhoea addressed the second proposed indication, treatment of primary dysmenorrhoea.

From those studies the Australian Drug Evaluation Committee (ADEC) considered that there was insufficient evidence of efficacy versus placebo for the acute pain indication. In particular, the withdrawal rate of patients from the single dose studies made it difficult to

assess the efficacy of celecoxib over an entire dosage period. The Committee noted that single dose studies were not generally acceptable as evidence of therapeutic efficacy.

Studies supporting Acute Pain in Adults following Surgery

Study A3191086

This was a prospective, randomized, double-blind, double-dummy, multicentre study comparing celecoxib and ibuprofen slow release (SR) in the management of acute pain post orthopaedic or gynaecological surgery. Its primary objective was to validate the analgesic efficacy of celecoxib compared with ibuprofen SR in the management of acute pain post orthopaedic or gynaecological surgery. Its secondary objective was to validate the safety of celecoxib compared with ibuprofen SR in the management of acute pain post orthopaedic or gynaecological surgery.

Twenty-four hours post surgery, patient controlled analgesia (PCA) was stopped and patients received celecoxib or comparator plus placebo, 2 doses approximately 12 hours apart whilst the background analgesia infusion continued. The PCA did not restart until the study treatment was administered. The background infusion and PCA varied with the investigating site (fentanyl 2 μg/mL or ropivacaine hydrochloride 1.2 mg/mL in 0.9% sodium chloride solution).

Endpoints

There were multiple endpoints with none designated as the primary endpoint: pain intensity as measured by categorical scale and visual analog scale (VAS), pain relief, the number of PCA demands (PCAd) and PCA effective (PCAe) doses, Patient's Global Evaluation of Study Medication and withdrawal due to the use of rescue medication.

Statistical methods

All efficacy data was summarized for the intention to treat (ITT) evaluable population.

Of note were the following:

· Due to changes that arose in the regulations of the Chinese State Food and Drug Authority (SFDA) during this study, formal statistical comparisons of changes from baseline (where applicable) and differences between treatment groups were conducted. Given the low power for detecting differences between treatment groups, the p-values should be interpreted with caution. In addition, no adjustments were made to the p-values for multiple testing.

· The inclusion of formal statistical tests of the changes from baseline in pain intensity measures and the comparison of treatment differences was considered a major change to the proposed analyses. These changes were included in the Statistical Analysis Plan (SAP) prior to database lock and study unblinding.

· The study was described as a registration study for China. This did not meet the requirements (as specified in the TGA-adopted EU guideline) of a non-inferiority or equivalence trial as there was no predefined primary endpoint, no statistical power determination of sample size, and no predefined margin. [1]

Patient enrolment, characteristics and disposition

This sample size was based on Chinese regulatory requirements and not on statistical considerations. The sex distribution was 52 (36%) males and 94 (64%) females. Details for each cohort were as follows:

· Celecoxib (n = 71): Mean age, 39.8 ± 10.6 years; Mean weight, 64.2 ± 11.1 kg.

[1] EMEA, September 1998. ICH Topic E 9: Statistical Principles for Clinical Trials. Note For Guidance on Statistical Principles for Clinical Trials. CPMP/ICH/363/96, 3.3.2.

- Ibuprofen (n = 75): Mean age, 39.2 ± 10.4 years; Mean weight, 64.4 ± 11.3 kg.

Primary efficacy results

There was no difference between treatment groups as shown on time-specific and time-weighted pain intensity difference (PID) scores by categorical scale and time-specific PID scores by VAS. Improvement in pain relief was comparable between celecoxib and ibuprofen at all times post-dose 1 apart from a significant treatment difference in favour of ibuprofen at 4 hours post-dose 1 ($p = 0.038$). However, this advantage was not sustained over time nor supported by the time-weighted pain relief scores.

A large proportion of subjects in each treatment group rated the study medication as good to excellent on the Patient's Global Evaluation of Study Medication: celecoxib 91%; ibuprofen 87%. The number of PCAd and PCAe doses was comparable between treatment groups at 8 and 24 hours post-dose 1. One subject in the ibuprofen group discontinued due to insufficient clinical response.

Comment

In 2002 ADEC indicated that the data in support of the pain indication were predominantly single dose studies and that submitted data were inadequate. There were 6 studies with multiple dosing, all≤ 5days with 625 patients receiving celecoxib.

This submission has added a study in which only two doses of celecoxib 12 hours apart were given. The active comparator, ibuprofen SR is not registered in Australia. Pain post surgery is not a registered indication for ibuprofen, although pain associated with dental procedures is. The statistical significance of the results is not great due to the sample size. Overall the study adds little to previous evaluations of submissions.

Other efficacy results – Literature Review

The evaluator noted that at least one of the published studies submitted in the literature review appears to have been a study that makes up part of this submission. It was not clear from the search description that the elimination step to remove such references was undertaken. There is thus the potential to bias the evaluation. Fortunately the study on this occasion did not affect the evaluation outcome.

There were three studies considered pivotal; all were randomised, double-blind, placebo-controlled trials that indicate their sample size calculations and statistical analyses, with the first 2 studies having a duration of 3 days post-operatively and the latter 5 days post-operatively (but only a 24 hour analysis of pain scores). All three studies used an 11 point score for pain analysis.

Pivotal studies

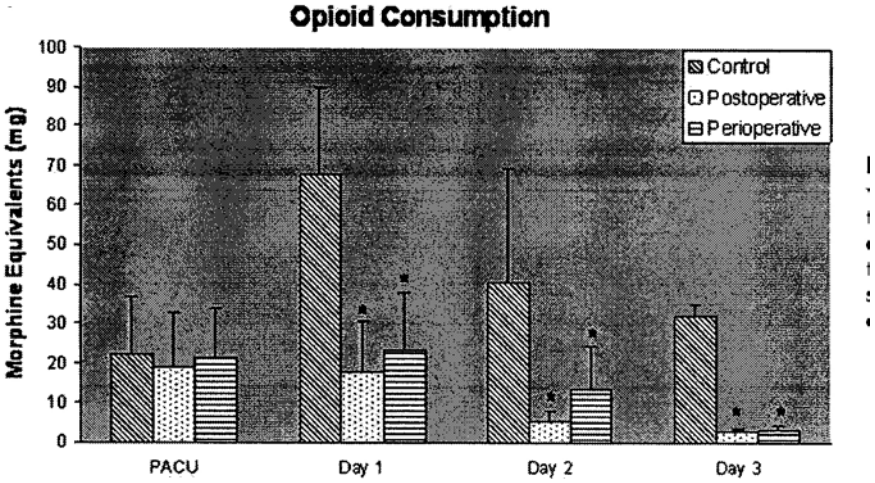
Sun et al tested the hypothesis that short-term administration of celecoxib would improve pain control and lead to an earlier resumption of normal activities of daily living after major plastic surgery without increasing wound complications.[2] The study had 40 patients taking celecoxib as an initial 400 mg dose post-operatively then 200 mg twice daily (bd) for 3 days, with a further 40 patients taking 400 mg pre-operatively then 200mg bd for 3 days. The primary variable - opioid analgesia use - was significantly less in the post-operative and peri-operative groups compared to the placebo group for the first three post-operative days (18 and 23 mg versus 68 mg, 5 and 13 mg versus 40 mg; and 3 and 3 mg versus 32 mg, respectively, $p < 0.05$) (Figure 1), as were the average pain scores. All patients had

[2] Sun T, Sacan O, White P, Coleman J, Rohrich R, Kenkel J. Perioperative versus postoperative celecoxib on patient outcomes after major plastic surgery procedures. Anesthesia Analgesia 2008; 106: 950-958.

bupivacaine infiltration at the end of surgery, and additional analgesia could be provided as fentanyl intravenous (IV) boluses, PCA morphine or hydrocodone.

As a result, pain scores were relatively low with the greatest difference (approximately 1.75) being at 4 hours and 24 hours.

Figure 1: Opioid consumption in converted morphine equivalents of the 3 groups during Post-Anaesthesia Care Unit (PACU) stay and on postoperative Days 1, 2, and 3.



Values are means ± standard deviations. *P < 0.05 versus control group.

White et al tested that post-operative administration of celecoxib would lead to an improved quality of recovery and earlier resumption of normal activities of daily living after laparoscopic surgery.[3] This study had 39 patients taking celecoxib 400 mg post-operatively then 200mg bd for 3 days and 38 patients taking placebo. It was noted that 133 were screened and 53 were excluded for lack of consent or lack of English. Thus there were originally 40 per group but there was incomplete follow-up data on three patients. The primary variable was the time to resume normal dietary habits (3 ± 2 days versus 2 ± 2 days), bowel function (3 ± 2 days versus 2 ± 1 days) and physical activities (6 ± 3 days versus 4 ± 2 days). These last two were significantly and clinically different. The effect on pain management was assessed by pain score and rescue analgesia requirements. Pain scores on the first, second and third days were significantly lower in the celecoxib group versus placebo. The differences at 24 hours, 48 hours and 72 hours were 2, 2 and 1 respectively. The corresponding percentages of patients requiring rescue analgesia were similarly significantly lower with 21%, 15% and 12% versus 30%, 29% and 27% at 24 hours, 48 hours and 72 hours, respectively.

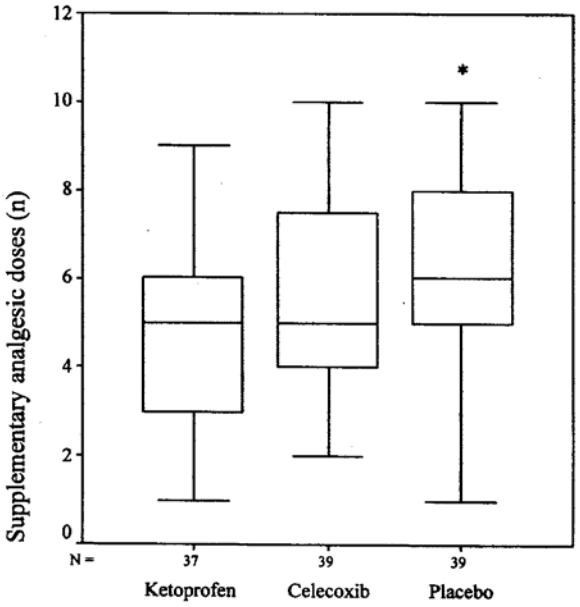
Nikanne et al evaluated the analgesic efficacy and safety of celecoxib in the management of pain after tonsillectomy.[4] This study had 40 patients taking celecoxib 200 mg or ketoprofen 100 mg or placebo pre-operatively then bd dosing for 5 days then as necessary (prn). The primary outcome parameter was the consumption of rescue analgesics during the first 24 hours after surgery. All patients in the celecoxib group, 32 of 37 patients (86%) in the ketoprofen group (p = 0.024, celecoxib versus ketoprofen) and 37 of 39 patients (95%) in the placebo group were provided with oxycodone for rescue analgesia during the first 4 hours after surgery. In the celecoxib group, the time to the first dose of rescue analgesic was significantly shorter than in the ketoprofen group (p= 0.039) (Figure 2). All patients were provided with rescue analgesia during the first 24 hours after surgery. The total number of oxycodone doses was 215 (mean 5 [range 2-14]) in the celecoxib group, 179 (5[1-9]) doses in the ketoprofen group, and 230 (6 [1-13]) doses in the placebo group (p = 0.021, placebo versus ketoprofen). Pain scores were only taken to 24 hours when there was no significant

[3] White PF, Sacan O, Tufanogullari B, Eng M, Nuangchamnong N, Ogunnaike B. Effect of short-term postoperative celecoxib administration on patient outcome after outpatient laparoscopic surgery. Can J Anaesth 2007; 54: 342-348.

[4] Nikanne E, Kokki H, Salo J, Linna TJ. Celecoxib and ketoprofen for pain management during tonsillectomy: a placebo-controlled clinical trial. Otolaryngology Head Neck Surg 2005; 132: 287-94.

difference from the placebo group. The study continued out to 3 weeks with all patients taking celecoxib or ketoprofen. The patients recorded the cumulative celecoxib/ketoprofen and paracetamol-codeine doses, the number of days with post-operative pain, the first day with no pain during drinking and eating, and the number of nights with awakenings due to post-operative pain. Patients were also asked whether the pain relief had been achieved and whether there were any problems in taking the capsules or tablets. At the end of the first week, 44 of 65 (67%) patients used celecoxib on a regular basis compared to 37 of 41 (91%) patients using ketoprofen regularly (p = 0.002).

Figure 2: Box plots of supplementary analgesic doses during the first 24 hours



Showing 10th, 25th, 50th, 75th, and 90th centiles and outliers

* P = 0.021, placebo compared to ketoprofen, Mann-Whitney test with Bonferroni correction.

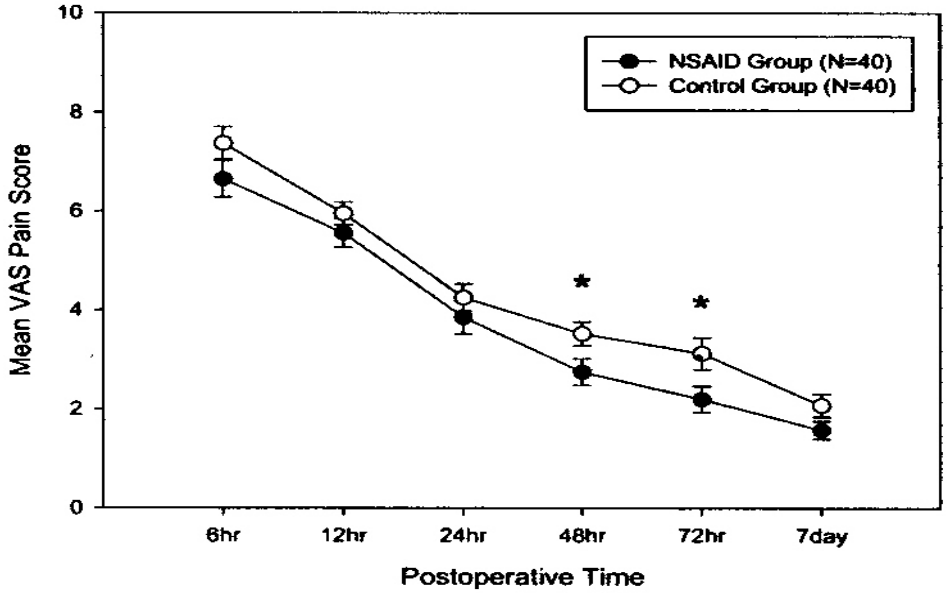
Supportive studies

All studies were double-blind, used an 11 point score for pain, and analysis, statistics and a population calculation was given - unless indicated.

The study by Huang et al was observer-blinded only.[5] It tested 40 patients taking celecoxib 400 mg pre-operatively then 200 mg bd for 5 days. PCA morphine use was significantly less compared with control. The visual analog scale for pain at rest (VAS_{rest}) was statistically less but only at 48 hours and 72 hours (when the greatest mean difference was 1.78 with control at ~3) (Figure 3). There was no difference in the visual analog scale for pain with walking ($VAS_{walking}$) with control.

[5] Huang Y, Wang C, Wang C, Lin W, Horng L, Jiang C. Perioperative celecoxib administration for pain management after total knee arthroplasty - a randomized, controlled study. BMC musculoskeletal disorders 2008; 9(epub): 77.

Figure 3: VAS Pain scores at rest



*: p value < 0.05. Error bar indicates standard deviation.

The study by Lim et al was unblinded.[6] It tested 164 patients taking celecoxib 200 mg versus diclofenac 100 mg every 12 hours. Three observations of VAS scores for pain at rest in the first 4 hours were significantly lower for celecoxib but the remaining 3 observations at eight, 12 and 24 hours, although lower, were not significantly different. The difference in pain score when mobilising was not significant.

The study by Watcha et al tested 60 patients taking celecoxib 200 mg pre-operatively, then 200 mg post-operatively versus rofecoxib (50 mg + 50 mg) versus paracetamol (2 g + 2 g) versus placebo.[7] Only the results at 24 hours were given. Rofecoxib patients used the least rescue analgesia (1 tablet[8], VAS = 0[8]) with celecoxib patients (2 tablets[8], VAS = 0[8]), paracetamol patients (3 tablets, VAS = 2[8]) and placebo tablets (3 tablets, VAS = 5) increasingly less effective.

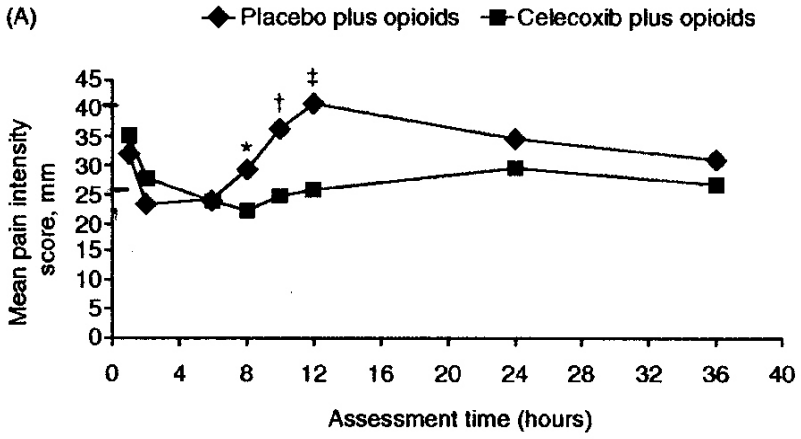
The study by Meunier et al tested 25 patients taking celecoxib 200 mg pre-operatively then 200 mg bd post-operatively for 3 weeks.[9] The study was placebo-controlled. The primary outcome was orthopaedic-related. The statistics plan and population calculation was not given (all secondary outcomes). All patients had osteoarthritis. Results were only presented in graphical form up to 14 days. In hospital VAS were similar, the only difference was at Day 14. Analgesic consumption at three weeks was lower in the celecoxib group.

The study by Ekman et al tested 99 patients taking celecoxib 400 mg pre-operatively then 200 mg once post-operatively.[10] It was placebo-controlled and employed a 100mm VAS measured to 36 hours. There were significant differences at 8, 10 and 12 hours with the

[6] Lim S, Tan P, Sockalingam J, Omar S. Oral celecoxib versus oral diclofenac for post-perineal repair analgesia after spontaneous vaginal birth: a randomised trial. ANZ J Obst Gynaecol 2008; 48: 71-77.
[7] Watcha M, Issioui T, Klein K, White P. Costs and effectiveness of rofecoxib, celecoxib, and acetaminophen for preventing pain after ambulatory otolaryngologic surgery. Anesthesia and analgesia 2003; 96: 987-994.
[8] Statistically significant versus placebo
[9] Meunier A, Lisander B, Good L. Effects of celecoxib on blood loss, pain, and recovery of function after total knee replacement: a randomized placebo-controlled trial. Acta Orthopaedica 2007; 78: 661-667.
[10] Ekman EF, Wahba M, Ancona F. Analgesic efficacy of perioperative celecoxib in ambulatory arthroscopic knee surgery: a double-blind, placebo-controlled study. Arthroscopy: 2006; 22: 635-642.

maximum difference of ~15 mm at 12 hours when placebo was ~40 mm (Figure 4). There was also a significant difference in opioid use from 10 to 24 hours.

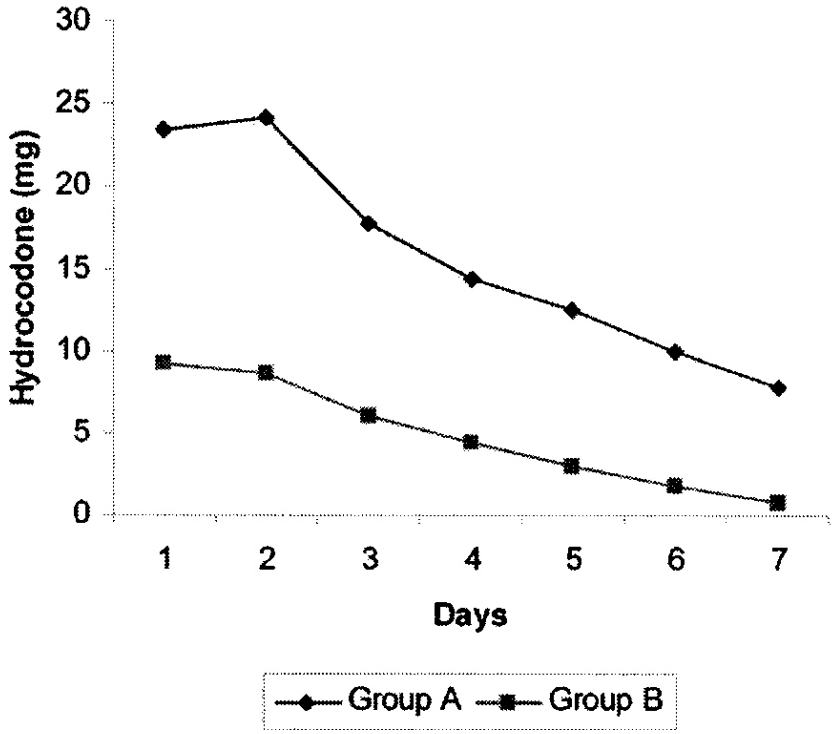
Figure 4: Patient's assessment of pain (A) at rest (mITT population)



*P = .045. †P = .002. ‡P < .001.

The study by Freedman et al was an open label study.[11] It tested 40 patients taking celecoxib 400 mg pre-operatively then 400 mg each morning post-operatively for 7 days. It was placebo-controlled. There was significantly less analgesic use and lower pain scores (average and daily - graphic details only) in the celecoxib group (Figure 5). The population calculation was not given.

Figure 5: Hydrocodone use during 7-day postoperative period



[11] Freedman BM, Balakrishnan TP, O'Hara EL. Celecoxib reduces narcotic use and pain following augmentation mammaplasty. Aesthet Surg J 2006; 26: 24-28.

The study by Pilatti et al tested 20 patients in a randomised crossover study described as double- masked.[12] However, while placebo and comparator (dexamethasone 4 mg) were given at the same times (1 hour pre-operatively and 8 hours post-operatively), celecoxib 200mg was given 1 hour pre-operatively and 12 hours post-operatively. The population size calculation was not given. Rescue medication use was the same across groups but pain scores were reported to be significantly lower for celecoxib than placebo in the first 4 hours and for some of the parameters beyond that to 7 hours.

The VAS (10 cm) achieved a maximum mean at 3 hours of 25.47 for the placebo group when it was 4.36 for the celecoxib group. The corresponding 101 numerical rating results were at 3 hours with 22.47 for the placebo group and 4.84 for the celecoxib group. Graphical depiction suggests the pain levels were low. This article used a 10cm VAS scale but gave results of up to 25.5 for the VAS.

Study not supporting:

The study by Karst et al tested 17 patients taking celecoxib as an initial 200 mg the night before surgery, then 200 mg pre-operatively and then 200 mg bd post-operatively for 24 hours.[13] It was placebo-controlled. There was no significant difference in any additional analgesic requirement or VAS (measured on post-operative Days 1 and 2 and the discharge day).

Studies not evaluable:

A number of studies were not evaluable for a variety of reasons including the availability of an abstract only,[14,15,16] the study was in the form of a letter,[17] and individual component comparison was not possible.[18]

Studies not evaluated:

A number of studies were not evaluated because they were single dose studies or dental single dose studies.

Dose ranging studies:

The study by Recart et al was a double-blind, placebo-controlled single dose study of 30 patients taking celecoxib 200 mg versus 30 patients taking 400 mg versus 30 patients taking placebo given pre-operatively.[19] The statistical plan and population calculation were

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[12] Pilatti GL, André-dos Santos F, Bianchi A, Cavassim R, Tozetto CW. The use of celecoxib and dexamethasone for the prevention and control of postoperative pain after periodontal surgery. J Periodontol 2006; 77: 1809-1814.

[13] Karst M, Kegel T, Lukas A, Lüdemann W, Hussein S, Piepenbrock S. Effect of celecoxib and dexamethasone on postoperative pain after lumbar disc surgery. Neurosurgery 2003; 53: 331-336.

[14] Tian J, Zu Q, Xiang L, Liu X, Cao Y, Zhou D. Analgesic outcome of taking celecoxib by time medicine method following total knee arthroplasty. Chin J Clin Rehab 2006; 10: 39-41.

[15] Brugger AM, Richardson ET, Drupka DT, et al. Comparison of celecoxib, hydrocodone/acetaminophen, and placebo for relief of post-surgical pain. 18th Ann Sci Meeting Am Pain Soc 1999; (October 21).

[16] Shirota T, Ohno KS, Michii K, I, Kamijo R, Nagumo M, Sato H, et al. A study of the dose-response of YM177 for treatment of postsurgical dental pain. Oral Therapeutics & Pharmacology 2001; 20: 154-172. (abstract)

[17] Ekman E, Berger M, Bhadra P. Letter to the Editor. Arthrosc J Arthrosc Relat Surg 2006; 22: 804.

[18] Iohom G, Abdalla H, O'Brien J, Szarvas S, Larney V, Buckley E, et al. The associations between severity of early postoperative pain, chronic postsurgical pain and plasma concentration of stable nitric oxide products after breast surgery. Anesthesia Analgesia 2006; 103: 995-1000.

[19] Recart A, Issioui T, White PF, Klein K, Watcha MF, Stool L, et al. The efficacy of celecoxib premedication on postoperative pain and recovery times after ambulatory surgery: a dose-ranging study. Anesthesia Analgesia 2003; 96: 1631-1635.

provided. There was a significant difference in decreased use of post-operative rescue medication compared to placebo for both doses and also between 400 mg and 200 mg celecoxib. There was mostly no difference in an 11 point verbal rating scale (VRS).

Studies Supporting Acute Pain in Adults following Musculoskeletal and/or Soft Tissue Injury

1. Ankle sprain:

Multicentre, double blind, placebo controlled, randomised, parallel group studies in ankle sprain to compare the efficacy and tolerability of celecoxib with a maximum dose of 200 mg bd:

- versus ibuprofen: Study N49-00-06-127 - SUCCESS IIA - 148 patients over 10 days duration.
- versus naproxen: Study I49-01-06-138 - SUCCESS-IIC - 199 patients, 7 days.
- versus diclofenac: Study I49-02-06-154 - SUCCESS-IID - 221 patients, 7 days.
- versus ibuprofen: Study I49-02-06-155 - SUCCESS-IIE - 211 patients, 8 days.
- versus diclofenac slow release: Study I49-01-02-189 - SUCCESS-IIG - 189 patients, 7 days, initial dose 400 mg.

Study A3191332 - an open label randomised multicentre comparative study on celecoxib efficacy and safety versus non-selective non-steroidal antiinflammatory drugs (NSAIDs) in acute pain due to ankle sprain. Dosage was 400 mg initially then 200 mg bd. It involved 141 patients and the duration was 7 days.

2. Shoulder pain:

Study N49-01-06-201 - Randomised, double blind, multicentre, parallel group study to compare the efficacy and safety of celecoxib and naproxen versus placebo in patients with acute tendonitis and/or bursitis of the shoulder. Dosage was 400 mg initially then 200 mg bd. It involved 98 patients and the duration was 14 days.

Study F49-98-02-122 - Comparison of the efficacy of celecoxib 200 mg bd versus naproxen in the treatment of acute shoulder pain involving 99 patients over 14 days.

3. Low back pain

Study A3191064 - A multicentre, randomised, double-blind, double-dummy study of the safety, tolerability and efficacy of celecoxib 200 mg twice a day (with a 400 mg attack dose) versus sodium diclofenac in subjects with acute low back pain involving 123 patients over 7 days.

Pivotal studies - SUCCESS

Study N49-00-06-127 SUCCESS IIA

The primary objectives of this study were to determine whether 10 days of treatment with celecoxib 200 mg bd was superior to placebo and at least as effective as ibuprofen 800 mg three times daily (tds) in patients with acute ankle sprain.

The inclusion criteria were patients who had sustained, no more than 48 hours prior to the first dose of study medication, a first or second degree ankle sprain of the lateral aspect, specifically: i) anterior talofibular ligament and/or ii) calcaneofibular ligament. Such patients presented with moderate-severe ankle pain, that is, the Patient's Assessment of Ankle Pain VAS 45 mm, on full weight bearing.[20]

[20] The Patient's Global Assessment of Ankle Injury uses a 5 point scale as follows:

1: Very Good - no symptoms and no limitation of normal activities, 2: Good - mild symptoms and no limitation of normal activities, 3: Fair - moderate symptoms and limitation of some normal activities, 4: Poor - severe symptoms and inability to carry out most normal activities, 5: Very Poor - very severe symptoms that were intolerable and inability to carry out all normal activities.

The study was a 10 day randomized, double-blind, placebo-controlled, parallel group study comparing the efficacy and safety of celecoxib and ibuprofen in patients with acute first- or second-degree lateral ankle sprain.

At baseline, a complete medical history and an abbreviated physical examination was performed, with ankle pain and function/activity assessments including the Physician's Global Assessment of Ankle Injury; the Patient's Global Assessment of Ankle Injury; the Patient's Assessment of Normal Function/Activity; and the Patient's Assessment of Ankle Pain VAS.[21,22] In addition to the traditional rest, ice, compression, and elevation (RICE) treatment for ankle sprain, patients were allowed to receive other therapeutic modalities for ankle sprain. Patients completed a diary recording study medication taken, any over-the-counter and prescription medications taken, the Patient's Assessment of Normal Function/Activity, and, on Day 8, the Patient's Global Assessment of Ankle Injury and the Patient's Assessment of Ankle Pain VAS.

Endpoints

Primary measures of efficacy were the Patient's Global Assessment of Injury and VAS pain scale at Day 4. Secondary efficacy endpoints were multiple and were based upon celecoxib versus ibuprofen or placebo with respect to the time to return to normal function/activity, the Physician's Global Assessment of Injury, and the patient's and physician's satisfaction assessments.

Statistical methods

Two-sided 95% CIs were calculated for the (ITT) differences between placebo and each active treatment to assess their superiority over placebo. One-sided 95% CIs were calculated for the (evaluable cohort) differences between the two active treatments to assess the non-inferiority of celecoxib relative to ibuprofen. A 15% difference in responder rate[23] for Patient's Global Assessment of Ankle Injury was considered clinically significant.

Patient enrolment, characteristics and disposition

Based on a previous study which compared diclofenac/misoprostol and diclofenac alone in treating soft tissue injury of the ankle or knee, a 'responder rate' of 90% on the active treatments was assumed. The 150 patients per treatment arm would have at least 80% power to detect differences of 11.7 percentage points or more between either active treatment and placebo. Details of the treatment groups are as follows:

- Celecoxib: M/F 89(60%)/59(40%), mean age 31.3 ± 12.07 (range 18-83) years.
- Ibuprofen: M/F 96(62%)/59(38%), mean age 30.4 ± 10.50 (range 18–70) years.
- Placebo: M/F 83(58%)/59(42%), mean age 29.8 ± 11.9 (range 18-74) years.

Primary efficacy results

[21] The Physician's Global Assessment of Ankle Injury uses a 5 point scale as follows:
1: Very mild -very mild signs and symptoms of ankle sprain, 2: Mild - mild signs and symptoms of ankle sprain, 3: Moderate - moderate signs and symptoms of ankle sprain, 4: Severe - severe signs and symptoms of ankle sprain, 5: Very severe - very severe signs and symptoms of ankle sprain.

[22] The Patient's Assessment of Normal Function/Activity uses a 5 point scale as follows:
1: normal walking/activity and no pain, 2: normal walking/activity with pain, 3: mildly restricted walking due to pain and can't resume normal activities, 4: moderately restricted walking due to pain and can't resume normal activities, 5: severely restricted walking due to pain and can't resume normal activities.

[23] Improvement by at least one grade for Patient's Global Assessment of Ankle Injury; the proportions of patients improving by at least 20mm on the VAS scale.

Celecoxib non-inferiority to ibuprofen was demonstrated at Day 4 with respect to the Patient's Global Assessment of Ankle Injury and VAS (Table 1). Both celecoxib and ibuprofen showed statistical superiority over placebo. However, while the Patient's Global Assessment effect size for celecoxib versus placebo was 0.59 and for ibuprofen versus placebo 0.81, with VAS scores the differences with placebo were not clinically significant.

Table 1: Results Primary Variables (Evaluable Cohort).

Patient's Global Assessment of Ankle Injury Scores on Day 4 (Primary endpoint)				
	Celecoxib (N=147)		Ibuprofen (N=155)	Placebo (N=141)
Very good	4 (3%)		5 (3%)	3 (2%)
Good	43 (29%)		49 (32%)	25 (18%)
Fair	81 (55%)		79 (51%)	79 (56%)
Poor	18 (12%)		19 (12%)	28 (20%)
Very poor	1 (1%)		4 (3%)	6 (4%)
Treatment Differences	**effect size**	**Odds Ratio**	**95% CI**	**p-value**
Celecoxib vs Placebo	0.72 ± 0.23	2.06	1.30, 3.25	0.002
Celecoxib vs Ibuprofen	-0.00 ± 0.22	1.00	0.69[a]	0.990
Ibuprofen vs Placebo	0.72 ± 0.23	2.06	1.31, 3.25	0.002
VAS Scores on Day 4 (Primary endpoint)				
Mean ± SD (Unadjusted)	36.1 ± 21.00		38.0 ± 22.45	44.9 ± 20.66
LSM ± SE	36.4 ± 1.70		38.5 ± 1.66	43.6± 1.72
Treatment Differences	**Δ LSM ± SE**		**95% CI**	**p-value**
Celecoxib vs Placebo	-7.13 ± 2.36		-11.76, -2.49	0.003
Celecoxib vs Ibuprofen	-2.06 ± 2.29		1.71[b]	0.369
Ibuprofen vs Placebo	-5.07 ± 2.33		-9.65, -0.48	0.030

[a] Lower 95% confidence limit. The null hypothesis of non-inferiority of celecoxib vs. ibuprofen is accepted because this limit is > 0.33. The p-value is from the two-sided test for a difference between celecoxib and ibuprofen.
[b] Upper 95% CI. The hypothesis of non-inferiority of Celecoxib vs Ibuprofen is accepted because this limit is < 20mm. The p-value is from the two-sided test for a difference between Celecoxib and Ibuprofen.
SD: standard deviation

Study I49-01-06-138 SUCCESS-IIC

The primary objectives of this study were to determine whether 7 days of treatment with celecoxib 200 mg bd was as effective as naproxen 500 mg bd in patients with acute ankle sprain. The inclusion/exclusion criteria were similar to study 127. The population was calculated based on the same study as used in Study 127. The primary (Day 4) and secondary endpoints were the same as for Study 127. The treatment groups were as follows:

- Celecoxib: M/F 110(50%)/112(50%), mean age 33.8 ± 13.32 (range 18-80) years.
- Naproxen: M/F 116(51%)/112 (49%), mean age 32.3 ± 11.65 (range 18–80) years.

Primary Efficacy Results

The non-inferiority of celecoxib to naproxen was demonstrated at Day 4 with respect to the Patient's Global Assessment of Ankle Injury and VAS (Table 2).

Table 2: Patient's Global Assessment of Ankle Injury Scores on Day 4.

	Celecoxib (N=198)		Naproxen (N=198)	
Very good	11 (6%)		13 (7%)	
Good	56 (28%)		59 (30%)	
Fair	106 (54%)		106 (54%)	
Poor	23 (12%)		18 (9%)	
Very poor	1 (1%)		1 (1%)	
Treatment Differences	**effect size**	**Odds Ratio**	**95% CI**	**p-value**
Celecoxib vs Naproxen	-0.13	0.87	0.59, 1.29	0.497
VAS Scores on Day 4 (Primary endpoint) ITT				
Mean ± SD (Unadjusted)	33.0 ± 18.23		29.8 ± 18.19	
LSM ± SE	31.9 ± 1.96		29.0 ± 1.91	
Treatment Differences	**Δ LSM ± SE**		**95% CI**	**p-value**
Celecoxib vs Naproxen	2.90 ± 1.69		-0.43, 6.23	0.087

SD: standard deviation

Study I49-02-06-154 SUCCESS-IID

The primary objectives of this study were to determine whether 7 days of treatment with celecoxib 200 mg bd is as effective as diclofenac 75 mg bd in patients with acute ankle sprain. The inclusion/exclusion criteria were similar to study 127. The population was calculated based on the same study as used in Study 127. The primary (Day 4) and secondary endpoints were the same as for Study 127. The treatment groups were as follows:

- Celecoxib: M/F 133(67%)/66(33%), 188 completed, mean age 29.5 ± 10.96 (range 18-76) years.
- Diclofenac M/F: 133(67%)/66(33%), 184 completed, mean age 30.6 ± 12.71 (range 18–90) years.

Primary Efficacy Results

The non-inferiority of celecoxib to diclofenac was demonstrated at Day 4 with respect to the Patient's Global Assessment of Ankle Injury and VAS.

Study I49-02-06-155 SUCCESS-IIE

The primary objectives of this study were to determine whether 8 days of treatment with celecoxib 200 mg bd was as effective as ibuprofen 400 mg tds in patients with acute ankle sprain. The inclusion/exclusion criteria were similar to study 127. The population was calculated based on the same study as used in Study 127. The primary (Day 4) and secondary endpoints were the same as for Study 127. The treatment groups were as follows:

- Celecoxib: M/F 133(67%)/66(33%), 188 completed, mean age 29.5 ± 10.96 (range 18-76) years.
- Ibuprofen: M/F 133(67%)/66(33%), 184 completed, mean age 30.6 ± 12.71 (range 18–90) years.

Primary Efficacy Results

The non-inferiority of celecoxib to ibuprofen was demonstrated at Day 4 with respect to the Patient's Global Assessment of Ankle Injury and VAS.

Study I49-01-02-189 SUCCESS-IIG

This study was not evaluated for efficacy because the active comparator (diclofenac SR 75 mg) has not been registered in Australia.

There appears to be three published papers based on these ankle studies.[24,25,26] The first two papers were not submitted, only abstracts were viewed and the third was an abstract which was possibly a conference paper presentation:

Study A3191332

This was an open label randomised multicentre comparative study on celecoxib efficacy and safety versus non-selective NSAIDs in acute pain due to ankle sprain. Celecoxib dosage was 400 mg initially then 200 mg bd for 141 patients over 7 days. This study was not evaluated because there were multiple active comparators.

Study N-49-01-02-201

This was a randomized, double-blind, parallel group study to compare the efficacy and safety of celecoxib and naproxen versus placebo in patients with acute tendinitis and/or bursitis of the shoulder.

The primary endpoint was the Maximum Pain Intensity at Rest (using VAS) at Day 14, with multiple secondary endpoints (Table 4).[27] The study showed superiority of celecoxib over placebo ($p = 0.032$) but not for naproxen ($p = 0.077$). Individual patient data was not available. Withdrawals from lack of efficacy included 8 patients (8.2%) taking celecoxib, 11 patients (10.2%) taking placebo, compared with 3 (3%) taking naproxen.

Table 4: Maximum Pain Intensity at Rest

	Efficacy Variable	Placebo N=108	Celecoxib bd N=98	Naproxen bd N=100
Baseline	Mean Score (SD)	69.3 (13.77)	70.4 (13.10)	69.9 (14.99)
Day 7	Mean Score (SD)	50.9 (24.88)	42.8 (26.38)	43.5 (26.72)
	LS Mean Change (SD)(a)	-18.8 (27.37)	-27.2 (27.22)*	-26.5 (26.97)*
Day 14	Mean Score (SD)	44.3 (29.29)	35.5 (29.29)	36.8 (30.63)
	LS Mean Change (SD)	-25.8 (31.73)	-34.7 (30.29)*	-33.1 (29.48)

(a) LS mean change from Baseline. *Statistically significantly different from placebo at level < 0.05.
SD: standard deviation

[24] Petrella R, Ekman EF, Schuller R, Fort JG. Efficacy of celecoxib, a COX-2-specific inhibitor, and naproxen in the management of acute ankle sprain: results of a double-blind, randomized controlled trial. Clin J Sport Med. 2004; 14: 225-31.

[25] Ekman EF, Fiechtner JJ, Levy S, Fort JG. Efficacy of celecoxib versus ibuprofen in the treatment of acute pain: a multicentre, double-blind, randomized controlled trial in acute ankle sprain. Am J Orthop. 2002; 31: 445-51.

[26] Yepes JP, Ekman E, Levy SD. Efficacy of celecoxib versus diclofenac in the treatment of pain associated with ankle sprain: a multicentre, double blind, randomized, control trial. J Clin Rheumatol 2002; 77 [Abstr 113].

[27] The Pain Intensity Categorical Scale uses a 3 point scale based on the assessment of "My pain at the moment is" 0 = absent; 1 = mild; 2 = moderate; 3 = severe.

Study F49-98-02-122

This was a randomized, double-blind, double dummy, 2 parallel group study of 14-day treatment with celecoxib versus naproxen, with a 4-week follow-up in patients with acute tendinitis and/or bursitis of the shoulder.

The primary objective was to assess and compare the efficacy in terms of maximum pain intensity at rest (maximum daytime or nocturnal pain) of celecoxib 200 mg bd versus naproxen 500 mg bd given for 14 days in acute shoulder pain, excluding general traumatic and inflammatory disorders.

The secondary objectives were included to assess and compare the effects of celecoxib versus naproxen by:

- Analgesic efficacy on maximum pain intensity on mobilisation.
- Improvement in mobility.
- Improvement in the functional score (self-assessment of the level of daily activity by the Association of Shoulder and Elbow Surgeons [ASES] questionnaire).[28]
- Overall assessment of treatment by the patient and physician.
- The use of paracetamol (rescue medication).

There was a major variation to inclusion criteria after commencement of the study. The criterion of a patient presenting with an acute painful shoulder "with onset dating from ≤ 7 days" was altered to "with onset dating from≤ 14 days". This applied to 134 patients (60 in the celecoxib group and 74 in the naproxen group).

The analysis of covariance (ANCOVA) comparison of the maximal pain intensity at rest was made on the absolute change from baseline at Day 14 or withdrawal (Table 5). In the case of a missing value at Visit 2[29], the baseline value replaced the value at Visit 2. The delay between the last study treatment intake and the date of evaluation at Visit 2 was not taken into account. All values at Visit 2 were used whatever this delay was.

Table 5: Primary variable in ITT and PP Populations

Population	VAS at rest Day14-Day 0		Difference between groups	ANCOVA p-value	95% CIs of difference*
	Celecoxib (mean ± SD)	Naproxen (mean ± SD)			
Intent to treat (ITT)	N=99 - 47.9 ± 2.52	N=103 - 42.3 ± 2.47	-5.6	0.117	-12.52; 1.38
Per Protocol (PP)	N=94 - 49.4 ± 2.36	N=92 - 46.5 ± 2.38	-3.0	0.380	

* post hoc analysis.

The mean maximum rest pain was 68.4 ± 14.2mm (celecoxib) and 65.2 ± 14.7 (naproxen) on inclusion to the study. Sixty (62.5%) celecoxib and 55 (57.3%) naproxen patients took rescue

[28] The ASES questionnaire assesses functional activity using 10 daily activities with a three point scale as follows: 0 = impossible; 1 = very difficult; 2 = sometimes difficult; 3 = easy. Pain relief is assessed with a five point scale based on the assessment of "My relief from starting pain is": 0= None; 1= A little; 2= Some; 3= A lot; 4= Complete.

[29] This appears to be the only use of the undefined term Visit 2.

medication (Panadol) for a mean of 0.7 tablets/day in both groups. Appendices including individual patient data were not available.

The study report in relation to statistical analysis states "Since this study should have been designed as one-sided equivalence (non inferiority of celecoxib relatively to naproxen), the results of such an analysis are also presented". The sample size was based on a difference in maximum pain intensity at rest of 15 mm (VAS 0-100) which was considered clinically relevant.

Study A3191064

This was a Brazilian, multicentred, randomized, double-blind, double dummy study of the efficacy, safety, and tolerability of celecoxib 200 mg bd (after an initial 400 mg dose) versus sodium diclofenac 75 mg bd in subjects with acute low back pain. This study was published,[30] with the article included in the literature search.

The primary objective was to evaluate analgesic efficacy of celecoxib versus diclofenac sodium in subjects with acute low back pain.

The primary efficacy variable was the change from baseline at Day 3 (Visit 2) in the patient rated 0 (no pain) - 100 (worst pain) mm VAS Pain Intensity assessment.

Secondary efficacy variables included:

- the change in VAS Pain Intensity assessment at Study Day 7 from baseline
- the Categorical Pain Intensity at Study Day 3 and Day 7
- Pain Relief at Day 3 and Day 7
- Global Subject's Assessment at Day 3 and Day 7
- the subject's functional ability change at Day 7 from baseline (using the Roland Morris Questionnaire)[31]
- the subjects' health and quality of life change at Day 7 from baseline (using the Acute SF-36).[32]

The sample size of 100 subjects/arm was initially erroneously calculated to have 80% power for testing the non-inferiority hypothesis, based on one reference (not given). Correction of the calculations showed 143/group were needed. A more recent reference[33] then was used in calculations and this supported the use of 100 subjects/arm. Ten mm was considered to be the minimum clinically acceptable difference for declaring non-inferiority.

[30] Ralha LVDB, Oliveira L, Chahade W, Rangel P, Sun W. Efficacy and tolerability of celecoxib versus diclofenac: Results of a multicenter, randomized, double-blind, noninferiority study in subjects with acute low back pain. Rev Bras Med 2008; 65: 378-387.

[31] The Roland-Morris Questionnaire (RMQ) is a self-administered disability measure in which greater levels of disability are reflected by higher numbers on a 24-point scale.

[32] The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is available for two recall periods: standard (4-week recall) and acute (1-week recall).

[33] Vinueza R, Sands G, Martin A. Randomized, double blind, multicenter study of the safety and efficacy of valdecoxib 40 mg once daily vs. diclofenac 75 mg twice daily in subjects with acute low back pain. Clinical Study Report – Protocol A3471012. Pfizer Pharmaceutical Group. Nov. 24, 2004.

The per protocol (PP) population change from baseline at Day 3 in the VAS was assessed using an ANCOVA with effects for treatment, centre (fixed), and the baseline assessment as the covariate.

The use of rescue medication led to discontinuation from the study. There was one patient on celecoxib discontinued for a protocol deviation, the nature of which could not be determined from the data.

Primary efficacy results

The difference between VAS evaluations from baseline to Day 3 in the PP Population[34]; showed non-inferiority of celecoxib with respect to diclofenac sodium (-2.56 mm 95% CIs -7.67, 2.56) according to the predefined 10mm limit (Table 6).

Table 6: VAS Scores PP population

Mean ± SD (Unadjusted)	Celecoxib (N=114)	Ibuprofen (N=113)
Baseline	76.8 ± 12.11	76.3 ± 12.54
Day 3	36.3 ± 21.37	33.0 ± 19.96
Change from baseline	-40.5 ± 21.02	-43.3 ± 21.58
Change from baseline LSM ± SE	-40.00 ± 2.49	-42.55 ± 2.50
Treatment Differences	**Δ LSM ± SE**	**95% CI**
Diclofenac - Celecoxib	-2.56 ± 2.60	-7.67 to 2.56

Lower bound of 95% CI is > -10mm i.e. non-inferior. SD: standard deviation

Other efficacy results

Other efficacy results are shown in Table 7.

Table 7: Efficacy results expressed as difference (diclofenac- celecoxib)

Parameter	Day 3 Δ (95% CI)	Day 7 Δ (95% CI)
VAS change from baseline (mITT)	-2.62 mm (-7.55, 2.31)	-1.93 mm (-7.52, 3.66)
Categorical Pain Intensity score (mITT population)	-0.09 (-0.25, 0.06)	-0.05 (-0.25, 0.14)
Pain relief score (mITT population)	0.22 (0.01, 0.44)	0.10 (-0.18, 0.37)
Subject Global Assessment score (mITT population)	0.03 (–0.17, 0.22)	0.11 (-0.11, 0.32)

Study I49-99-06-078

This study was evaluated in a previous submission but is referred to in the sponsor's *Clinical Summary*. It was summarized in the minutes of the 220th ADEC meeting on 7-8 February 2002 as follows:

Study I49-99-06-078 was an acute non-surgical trial of 300 patients with acute lower back pain. It was an active comparator trial with slow release diclofenac 75 mg versus celecoxib 200 mg twice daily for 10 days. The primary endpoint was the area under the curve (AUC) for pain intensity (PI) rated on a daily basis. There was a low withdrawal rate for treatment failure. The mean AUC PI was lower for celecoxib than placebo on day five and day six only and was not significant compared to placebo on any day for VAS. There were no significant differences between celecoxib and placebo in the time to being pain free.

The evaluator noted that the active comparator, slow release diclofenac is not registered in Australia.

[34] The PP population was used for the analyses of the primary efficacy measure. The analysis of the primary efficacy measure was repeated using the modified intent to treat (mITT) population in a secondary analysis.

Other efficacy results – Literature Review

Two other references provided were not relevant to the indication.[35,36]

Conclusions regarding efficacy

I. Acute Pain in Adults following Surgery

ADEC has noted that single dose studies were not generally acceptable as evidence of therapeutic efficacy.

Study A3191086, as previously stated and for the reasons then given, adds little to previous evaluations of submissions. The evaluator believed there was sufficient evidence in the literature review to support the efficacy of celecoxib in pain following surgery. The placebo pain scores in the studies are low as a result of either minor surgical procedures or concomitant use of other analgesics. Thus differences that may be significant statistically do not have strong clinical implications.[37] There is also, however, a decrease in other analgesics used, which the evaluator considered sufficient evidence for efficacy.

The usual role of NSAIDs in acute pain is either for mild to moderate pain or as an adjunct in multi-modal treatment of severe pain, thus studies supporting its sole use in severe pain are unlikely.

There was, however, no good evidence provided to support the use of celecoxib for 10 days for post-surgical pain relief. The Meunier et al study had a duration of 3 weeks but the patients all had osteoarthritis and the Freedman et al study had a duration of 7 days, but was an open study. The Guidance document CPMP/EWP/612/00[38] require the duration of study for surgical pain to be up to 1 week.

The dosage recommended is supported by the studies, most of which used an initial dose of 400 mg then 200 mg bd and this is supported by the dose ranging study by Recart that found a single pre-operative dose of 400 mg was more effective than 200 mg.

II. Acute pain in adults following Musculoskeletal and/or Soft Tissue Injury

The literature review and some of the studies that were not evaluated were not pivotal to the evaluation. The evaluator believed there was sufficient evidence to support the efficacy in the use of celecoxib in adults following musculoskeletal and/or soft tissue injury. Initial VAS and subsequent falls were sufficiently high to readily show statistical efficacy however the changes relative to placebo in the primary endpoints were not clinically impressive. From these studies (127 and 201), most of the advantage of taking celecoxib or active comparator occurs early and while in study 201 statistical efficacy was shown for celecoxib at 14 days, this was not so for the comparator. The submitted indication of up to 10 days appears reasonable.

Safety

There was no overall summary of relevant studies submitted. While the 1998 submission was summarised, both the 2001 submission studies and the studies in this submission were

[35] Mets T, Bautmans I, Njemini R, Lambert M, Demanet C. The influence of celecoxib on muscle fatigue resistance and mobility in elderly patients with inflammation. Amer J Geriat Pharmacother 2004; 2: 230-238.

[36] Weckx LL, Ruiz JE, Duperly J, Mendizabal GA, Rausis MB, Piltcher SL et al. Efficacy of celecoxib in treating symptoms of viral pharyngitis: a double-blind, randomized study of celecoxib versus diclofenac. J Internat Med Res 2002; 30: 185-194.

[37] CPMP/EWP/252/03 Rev 1, doesn't define this but CPMP/EWP/612/00 (see below), page 6: Primary endpoints: In addition other responder definitions, like a 2-point reduction on pain intensity as compared to baseline (0-10 scale), could be subject of a sensitive analysis.

[38] EMEA, Committee for Proprietary Medicinal Products (CPMP), 21 November 2002. Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain, CPMP/EWP/612/00.

individually presented in relation to safety. In relation to the 2001 submission, the minutes of the 220th ADEC meeting stated that "no new safety issues were discussed". A summary of safety of these studies was submitted.

There was some combination review of all pain studies (Table 8).

Table 8: AEs with incidence≥ 3% in any treatment group - all 2001 pain studies

Adverse event	Placebo	Celecoxib	nsNSAIDs[a]	Opioids[b]
Number treated	806	1468	591	374
Any event	43.7	42.3	44.7	54.0
Body as a whole – general disorders				
Fever	5.6	2.5	3.0	2.9
Central and peripheral nervous system disorders				
Dizziness	5.0	4.1	3.2	9.1
Headache	8.9	8.1	7.1	7.8
Gastrointestinal disorders				
Abdominal pain	1.9	1.5	3.9	0.8
Alveolar osteitis	3.1	4.9	3.7	0.0
Diarrhoea	0.6	1.0	4.9	0.8
Nausea	11.7	12.4	14.4	15.8
Vomiting	6.5	5.6	7.1	8.0
Psychiatric disorders				
Somnolence	2.4	2.9	1.0	12.0

Data represent % patients.

[a] includes aspirin 650mg, ibuprofen 400mg, naproxen sodium 550mg and diclofenac SR 75mg

[b] includes propoxyphene napsylate 100mg/acetaminophen 650mg and hydrocodone 10mg/acetaminophen 1000mg.

In the celecoxib group there were significantly lower incidences of dizziness, nausea, vomiting, and somnolence compared to the combination opioid comparator group. There was one serious adverse event (SAE) reported for a celecoxib-treated patient that was considered by the investigator to be related to the drug. In the post-surgical pain studies, there was a higher incidence of withdrawal due to nausea (1.6%) and vomiting (1.6%) in the combination opioid group compared to the celecoxib group (0.4% for both).

Patient exposure

The sponsor's *Summary of Clinical Safety* referred to 1,131 patients treated with celecoxib at currently recommended doses in previously submitted studies post-surgery, with 119 in a previous back pain study. In the currently submitted studies 71 patients received celecoxib post-surgery with 1429 in musculoskeletal/soft tissue injury studies.

Adverse events

Pivotal studies

Study A3191086

There were two moderate adverse effects (AEs) considered related to celecoxib – nausea and headache – the latter led to discontinuation (due to AE) and no SAEs reported.

Success studies (SUCCESS IIA, IIC, IID, IIE, IIG)

Overall rates of AEs were lower for celecoxib than placebo with only a few individual systems showing a higher incidence (the greatest difference was in gastrointestinal [GI] system disorders - celecoxib 9.3% versus 8.5% placebo) (Table 9). There were no SAEs and 17 (1.8%) withdrawals due to AEs, all with celecoxib.

Table 9: Incidence of AEs by body system in SUCCESS studies

Body System Adverse Event (WHO)	**Placebo**	**Celecoxib 200mg bd**	**Naproxen 500mg bd**	**Diclofenac 75mg bd**	**Ibuprofen (tds)**	
					400mg	**800mg**
Treated patients, n	**141**	**966**	**198**	**409**	**208**	**155**
Any event, n (%)	**42 (29.8)**	**167 (17.3)**	**59 (29.8)**	**59 (14.4)**	**24 (11.5)**	**42 (27.1)**
Application site disorders	1 (0.7)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Autonomic nervous system disorders	2 (1.4)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Body as a whole – general disorders	7 (5.0)	23 (2.4)	12 (6.1)	9 (2.2)	2 (1.0)	8 (5.2)
Central and peripheral nervous system disorders	12 (8.5)	35 (3.6)	8 (4.0)	15 (3.7)	1 (0.5)	10 (6.5)
Endocrine disorders	2 (3.4)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)
Foetal disorders	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal system disorders	12 (8.5)	90 (9.3)	42 (21.2)	30 (7.3)	14 (6.7)	15 (9.7)
Hearing and vestibular disorders	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Heart rate and rhythm disorders	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Musculoskeletal system disorders	1 (0.7)	4 (0.4)	2 (1.0)	1 (0.2)	0 (0.0)	3 (1.9)
Platelet, bleeding & clotting disorders	1 (0.7)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	2 (1.4)	18 (1.9)	4 (2.0)	8 (2.0)	0 (0.0)	6 (3.9)
Resistance mechanism disorders	2 (1.4)	1 (0.1)	0 (0.0)	1 (0.2)	0 (0.0)	2 (1.3)
Respiratory system disorders	12 (8.5)	16 (1.7)	3 (1.5)	7 (1.7)	5 (2.4)	8 (5.2)
Skin and appendages disorders	2 (1.4)	10 (1.0)	1 (0.5)	1 (0.2)	2 (1.0)	0 (0.0)
Special senses other, disorders	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary system disorders	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.5)	0 (0.0)	1 (0.6)
Vascular (extracardiac) disorders	0 (0.0)	1 (0.1)	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Vision disorders	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.6)

Note: if a patient had more than one adverse event within a body system, that patient is counted once in the overall incidence for that body system.

Study N49-00-06-127

The mean duration of celecoxib exposure was 10.5 ± 1.75 days. The most common AEs were GI. Eight patients had 12 AEs probably related to celecoxib, all were GI except for two occurrences of rash (Table 10). There was one SAE of atrial fibrillation in association with celecoxib but it was considered unrelated. There was one discontinuation due to an AE in association with celecoxib, a moderate rash which was probably related to celecoxib.

Table 10: Incidence of AEs in≥ 2% of the patients in any treatment group by body system

Body System/Preferred Term	Celecoxib 200 mg bd (N=147)	Ibuprofen 800 mg tds (N=155)	Placebo (N=141)
Patients With At Least One AE	35 (24%)	42 (27%)	42 (30%)
Body as a Whole – General Disorders	7 (5%)	8 (5%)	7 (5%)
Injury – accidental	3 (2%)	2 (1%)	1 (1%)
Central and Peripheral Nervous System Disorders	5 (3%)	10 (6%)	12 (9 %)
Headache	5 (3%)	9 (6%)	10 (7%)
Gastrointestinal System Disorders	23 (16%)	15 (10%)	12 (9%)
Dyspepsia	8 (5%)	5 (3%)	2 (1%)
Diarrhoea	7 (5%)	3 (2%)	3 (2%)
Nausea	7 (5%)	2 (1%)	3 (2%)
Abdominal Pain	2 (1%)	3 (2%)	4 (3%)
Psychiatric Disorders	0 (0%)	6 (4%)	2 (1%)
Somnolence	0 (0%)	3 (2%)	1 (1%)
Respiratory System Disorders	4 (3%)	8 (5%)	12 (9%)
Sinusitis	1 (1%)	0 (0%)	3 (2%)
Upper respiratory tract infection	0 (0%)	4 (3%)	5 (4%)

Note: If a patient had more than one adverse event within a body system, the patient was counted only once in the overall incidence.

Study I49-01-06-138

The mean duration of celecoxib therapy was 7.8 ± 1.02 days. The most common AEs were GI (Table 11). Eleven patients had 15 AEs probably related to study drug, all were GI except for one occurrence of each of dermatitis and rash. There were no SAEs and three discontinuations due to an AE in association with celecoxib although the relationship was considered uncertain in each case.

Table 11: Incidence of AEs in≥ 2% of the patients in any treatment group by body system

Body System/Preferred Term	Celecoxib 200 mg bd (N=198)	Naproxen 500 mg bd (N=198)
Patients With At Least One AE	46 (23%)	59 (30%)
Gastrointestinal System Disorders	28 (14%)	42 (21%)
Abdominal Pain	10 (5%)	9 (5%)
Nausea	6 (3%)	9 (5%)
Diarrhoea	5 (3%)	7 (4%)
Dyspepsia	3 (2%)	12 (6%)
Flatulence	3 (2%)	4 (2%)
Central and Peripheral Nervous System Disorders	7 (4%)	8 (4%)
Headache	4 (2%)	6 (3%)
Body as a Whole – General Disorders	6 (3%)	12 (6%)
Fatigue	2 (1%)	4 (2%)
Injury – accidental	0 (0%)	3 (2%)
Psychiatric Disorders	7 (4%)	4 (2%)
Insomnia	3 (2%)	1 (1%)
Somnolence	3 (2%)	2 (1%)
Respiratory System Disorders	4 (2%)	3 (2%)
Rhinitis	3 (2%)	1 (1%)

Skin and Appendages Disorders	4 (2%)	1 (1%)
Rash	4 (2%)	1 (1%)

Study I49-02-06-154

The mean duration of celecoxib use was 7.8 (range 1-12) days. The most common AEs were GI (Table 12). Nine patients had 15 AEs probably related, all of which were GI except for two occurrences of headache, one of somnolence and one interaction with verapamil and/or ranitidine. There were no SAEs. There were three discontinuations due to AEs in association with celecoxib, two of which were considered probably related.

Table 12: Incidence of AEs. Patients with at least one dose of study medication

Adverse event (No. of patients in each category)	Celecoxib (n=221)	Diclofenac (n=228)
No. of adverse reactions	202 (91%)	210 (92%)
Headache	6 (3%)	2 (1%)
Abdominal pain	3 (1%)	4 (2%)
Gastritis	3 (1%)	3 (1%)
Influenza-like symptoms	2 (1%)	0 (0%)
Injury-accidental	2 (1%)	3 (1%)
Nausea	2 (1%)	0 (0%)
Diarrhoea	1 (0%)	0 (0%)
Dizziness	1 (0%)	1 (0%)
Hypotension	1 (0%)	0 (0%)
Somnolence	1 (0%)	1 (0%)
Verapamil/ranitidine interaction	1 (0%)	0 (0%)
Vomiting	1 (0%)	0 (0%)
Allergy	0 (0%)	1 (0%)
Insomnia	0 (0%)	1 (0%)
Polyuria	0 (0%)	2 (1%)
Rash	0 (0%)	1 (0%)

Note: AEs sorted by descending total incidence in the Celecoxib treatment group.

Study I49-02-06-155

The mean duration of celecoxib use was 6.7 ± 1.55 days. The most common AEs were GI (Table 13). Ten patients had 11 AEs probably related to study drug, all of which were GI, one of which was considered severe and five of which led to discontinuation. There were no SAEs. There were seven discontinuations due to AEs in association with celecoxib, five of which were considered probably related.

Table 13: Incidence of AEs. Patients with at least one dose of study medication

Adverse event (No. of patients in each category)	Celecoxib (n=211)	Ibuprofen (n=208)
No. of adverse reactions	189 (90%)	184 (88%)
Abdominal pain	5 (2%)	3 (1%)
Diarrhoea	3 (1%)	3 (1%)
Injury-accidental	3 (1%)	1 (0%)
Dyspepsia	2 (1%)	1 (0%)
Headache	2 (1%)	1 (0%)
Nausea	2 (1%)	2 (1%)
Blurred vision	1 (0%)	0 (0%)
Dysmenorrhoea	1 (0%)	0 (0%)
Flatulence	1 (0%)	1 (0%)
Gastritis	1 (0%)	0 (0%)
Haematoma	1 (0%)	1 (0%)
Hypertonia	1 (0%)	0 (0%)
Myalgia	1 (0%)	0 (0%)
Rash	1 (0%)	0 (0%)
Rash maculo-papular	1 (0%)	0 (0%)
Rhinitis	1 (0%)	0 (0%)
Tongue oedema	1 (0%)	0 (0%)
Urinary tract infection	1 (0%)	0 (0%)
Vertigo	1 (0%)	0 (0%)

Note: Adverse events are sorted by descending total incidence in the Celecoxib treatment group.

Study I49-01-02-189

The mean duration of celecoxib use was 8 (range 1-12) days. The most common AEs were GI (Table 14). Thirty four patients had AEs probably related, 17 of which were GI. There were no SAEs. There were three discontinuations due to AEs in association with celecoxib, one of which was considered probably related.

Table 14: Treatment-related AEs occurring in ≥ 2% of any treatment group

Adverse event by preferred term	Celecoxib N=189	Diclofenac SR N=181
Abdominal pain	7 (4%)	6 (3%)
Headache	5 (3%)	5 (3%)
Somnolence	5 (3%)	5 (3%)
Dyspepsia	3 (2%)	7 (4%)
Dizziness	3 (2%)	5 (3%)
Rhinitis	3 (2%)	1 (1%)
Flatulence	2 (1%)	3 (2%)
Nausea	2 (1%)	3 (2%)

Other studies

Study A3191332

The mean duration of celecoxib use was 7 (range 1-9) days. The most common AEs involved the nervous system. Ten patients had 11 AEs probably related to study drug, all of which were GI except for one occurrence of peripheral oedema. There were no SAEs. There was

one discontinuation due to an AE in association with celecoxib which was considered unrelated.

Study N-49-01-02-201

The duration of exposure was only given as individual data and listing of discontinuations. Based on the latter there was a mean duration of 13.3 (range 2-14) days. The most common AEs were GI. Ten patients had 13 AEs probably related to the study drug, most of which were GI, two of which were severe and four of which led to discontinuation. There were no SAEs. There were five discontinuations due to AEs in association with celecoxib, four of which were considered related.

Study F49-98-02-122

The mean duration of celecoxib use was 14.2 ± 2 (range 3-19) days. The most common AEs were GI. Twenty four (24.2%) patients had 36 AEs considered related, most of which were GI. There was one SAE; erosive bulbitis that was considered study drug-related. There were three discontinuations due to AEs in association with celecoxib which consisted of two occurrences of epigastric pain and one of urticaria, all of which were considered related.

Study A3191064

The mean duration of celecoxib use was 6.8 (range 2-7) days. The most common AEs were GI. Eighteen patients had 22 AEs considered study drug-related, most of which were GI, one of which was severe and three led to discontinuation. There were no SAEs. There were four discontinuations due to AEs in association with celecoxib, three of which were considered study drug-related.

Literature search – Safety - Acute Pain in Adults following Surgery

Of the pivotal studies:

- Sun et al reported a slightly lower or similar incidence of nausea and/or vomiting compared to placebo. There was one report of deep vein thrombosis in association with celecoxib.
- White et al reported similar incidence of nausea/vomiting (22% placebo versus 28% celecoxib in the PACU and 20% versus 20% post discharge).
- Nikanne et al reported significantly greater blood loss with placebo but the means were insignificant clinically (5 mL versus 20 mL) and the ranges were similar. There was one primary and five secondary bleeds in association with ketoprofen versus one secondary bleed in association with celecoxib and none on placebo.

Of the supporting studies:

- Huang et al reported nausea/vomiting at 43% in association with control (no placebo) and 28% in association with celecoxib with no significant differences in blood loss intra- or post-operatively.
- Lim et al reported a significant difference in upper GI symptoms for diclofenac versus celecoxib.
- Watcha et al reported no significant difference in nausea/vomiting between celecoxib, placebo, rofecoxib or acetaminophen.
- Meunier et al reported blood loss to be similar to placebo.
- Ekman et al reported opioid-related adverse effects were greater with placebo.
- Freedman et al reported that the incidence of haematoma was similar but there was less nausea with celecoxib compared to placebo.
- Pilatti et al reported no AEs.

· Karst et al reported that 12% had nausea/vomiting and sedation in association with placebo versus 23% in association with celecoxib.

Comment

In many of the trials opioids were used as needed concomitantly with the trial drug. Thus with placebo there is likely to be a greater demand for opiates. Hence it might be expected that there would be a greater incidence of opioid side effects, for example nausea and vomiting.

Adverse reactions (drug-related adverse events)

Nikanne et al commented that nine patients reported symptoms of hypersensitivity reactions with celecoxib. As celecoxib contain sulphonamide, there is a risk for hypersensitivity reactions.

Withdrawals due to adverse events

Overall withdrawal rates due to AEs were said to be low across all treatment groups, but summary data was not provided.

Deaths and other serious adverse events

There were no deaths reported for celecoxib-treated patients that were considered by the investigator to be related to celecoxib. As discussed above, one SAE (erosive bulbitis) was considered drug-related in association with celecoxib.

Laboratory abnormalities

Where reported there were no clinically meaningful changes in laboratory values noted in the laboratory shift tables or laboratory shift plots.

Effect on Vital Signs and Electrocardiograms

Where reported there were no clinically meaningful changes in vital signs.

Post-marketing experience

Post marketing information was not greatly relevant. The overall data showed most AEs occurred after a short duration of treatment (34% on Day 1, 30% on days 2-7, with a further 18% on days 7-14).

A search of the safety database showed 165 (15%) cases associated with painful conditions as an indication. There was no breakdown of that group.

Conclusions regarding safety

The cardiovascular risk of long term therapy was discussed in the sponsor's *Clinical Overview*, and the Precautions section of the PI quoted in relation to increased risk with increased duration.[39]

In the submission there was no discussion of the risk of post-surgical thrombotic episodes both in relation to the types of surgery studied and in other types of surgery - despite there already being a PI Contraindication for post-bypass surgery. Cardiovascular risks and benefits were not discussed in the sponsor's *Overview*, the sponsor's *Clinical Summary*, or the literature search and none referred to an editorial which discusses this concept.[40]

After, in the body of the article, offering a possible mechanism for the post bypass coronary thrombosis, decreased opposition to the vasoconstrictor and platelet aggregation caused by thromboxane release, the authors wrote:

[39] The results in the Safety Database appear to contradict the statement in the PI about the time of onset, that is, most AEs occur after a short duration according to the former which if it holds true then it is of concern for the proposed indications.

[40] Jones SF, Power, I. Postoperative NSAIDs and COX-2 inhibitors: cardiovascular risks and benefits. Brit J Anaesth 2005; 95: 281–284.

"However, endothelial prostacyclin, albeit counter intuitively, appears to be synthesized primarily by the 'inducible' COX-2 and therefore is inhibited by this group of drugs. Thus selective COX-2 inhibitors tip the balance in the opposite direction to aspirin, preserving haemostasis but potentially at the expense of increased vascular occlusion."

The authors at the end recommend:

"Meanwhile, we must avoid COX-2 selective agents in patients after recent coronary artery bypass graft (CABG) surgery and probably also after other procedures with an arterial anastomosis, such as vascular surgery, free tissue transfer and solid organ transplantation. We should probably choose a non-selective NSAID in preference to a selective agent in patients with, or with conditions increasing the risk of, cardiovascular disease unless there are other overriding considerations."

In the literature submitted there was only one study (Sun et al) that may have included some flap formation (abdominoplasty) and none that appeared to include grafts. Coincidentally that study had an episode of deep vein thrombosis in a patient taking celecoxib.

In the publication Acute Pain Management, the following was noted:[41]

"The question has been raised whether COX-2 inhibitors can produce a tendency to thrombosis because they inhibit endothelial prostacyclin production but spare platelet thromboxane synthesis and aggregation. While the pharmacological evidence for a prothrombotic effect of COX-2 inhibitors is plausible, the published data on the clinical risk are conflicting (Clark et al 2004)."

The section below was on cardiovascular risks rather than graft risks.

The December 2007 update to this edition deleted this paragraph and also inserted:

"However, short-term use of parecoxib and/or valdecoxib after non-cardiac surgery does not increase the risk of cardiovascular adverse events".[42]

The reference was to a Pfizer supported unpublished study (Schug et al 2009)[43] that looked at 8511 patients in 17 parecoxib and 15 valdecoxib studies that included no graft surgery. In the discussion Schug et al argue for the high shear stress of the cardiopulmonary bypass pump as being responsible for the incidence of increased CV thromboembolic risk seen in the CABG studies.

Clinical Summary and Conclusions

The evaluator recommended that, subject to modification, approval be given for the submitted extensions of indications. There were a number of additional recommendations:

1. The extensions of indications be inserted in the PI separately.

2. That in relation to the indication "acute pain in adults following musculoskeletal and/or soft tissue injury' this be approved for 10 days as submitted.

The evaluator believed there was sufficient evidence to support the efficacy in the use of celecoxib in adults following musculoskeletal and/or soft tissue injury. Initial VAS and subsequent falls were sufficiently high to readily show statistical efficacy however the changes relative to placebo in the primary endpoints were not clinically impressive. From these studies (127 and 201) most of the advantage of taking celecoxib or active comparator

[41] Acute Pain Management Scientific Evidence from ANZ College of Anaesthetists and Faculty of Pain Medicine second Edition July 2005 – endorsed by NHMRC.

[42] Schug, SA, Camu, F, Joshi, G, et al. 2007 Level I. Parecoxib – getting to the heart of the matter. Anaesthesia 2007; 62: 291-292.

[43] Schug, SA, Camu, F, Joshi, G, et al. Cardiovascular safety of the cyclooxygenase-2 selective inhibitors parecoxib and valdecoxib in the postoperative setting: An analysis of integrated data. Anesth Analg 2009; 108: 299-307.

occurs early. The submitted indication of up to 10 days appears reasonable. There appeared to be no new safety concerns in relation to this indication.

3. That in relation to the indication "acute pain in adults following surgery" this be approved for 7 days (not 10 as requested)[44] and there be inserted a warning in relation to the risk of thrombosis in arterial anastomosis, free tissue transfer and solid organ transplantation.[45]

This recommendation for approval is, as outlined above, based for efficacy on the literature review in the submission and not the submitted study. The evaluator believed there was sufficient evidence in the literature review to support the efficacy of celecoxib in pain following surgery. The placebo pain scores in the studies are low as a result of either minor surgical procedures or concomitant use of other analgesics. Thus differences that may be significant statistically do not have strong clinical implications. There is also however, a decrease in other analgesics used, which the evaluator considered sufficient evidence for efficacy. There was however no good evidence provided to support the use of celecoxib for 10 days for post-surgical pain relief. The Meunier et al study had a duration of 3 weeks but the patients all had osteoarthritis, the Freedman et al study had a duration of 7 days, but was an open study. CPMP/EWP/612/00 recommends the duration of study for surgical pain as up to 1 week.[38]

The evaluator noted that the National Prescribing Service website appears to be promoting the use of celecoxib for post-operative pain in its Feb/April 2007 documents: NPS acute postoperative pain (APOP) drug use evaluation (DUE) toolkit.[46,47,48,49]

V. Pharmacovigilance Findings

Risk Management Plan

The Risk Management Plan (RMP) was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM). No new safety concerns specific to the indication of treatment of acute pain were identified by the sponsor. Thus, there are no potential or identified risks, or areas of missing information presented in the submitted RMP. The sponsor proposes routine pharmacovigilance and routine risk minimisation (including information in the PI) for all safety issues. However, in the opinion of the OMSM evaluator there may be an increase in the potential for off-label use, particularly paediatric off-label use.

Overall, the RMP was acceptable.

There were two issues identified:

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[44] There was no good evidence provided to support the use of celecoxib for 10days for post surgical pain relief. Meunier et al study went for 3 weeks but the patients all had osteoarthritis, Freedman et al went for 7days, but was an open study. CPMP/EWP/612/00[44], gives the duration of study for surgical pain as up to 1 week.

[45] F. Jones & I. Power Postoperative NSAIDs and COX-2 inhibitors: cardiovascular risks and benefits British Journal of Anaesthesia 95 (3): 281–4 (2005).

[46] The APOP DUE toolkit is a quality improvement tool to assist hospital surgical, anaesthetic, pharmacy and nursing staff working with surgical patients to conduct an audit of patient care in the area of acute postoperative pain.

[47] http://www.nps.org.au/__data/assets/pdf_file/0014/70052/OKA5301_NPS_APOP_EVC_FINAL.pdf.

[48] http://www.nps.org.au/__data/assets/pdf_file/0012/70014/OKA5496_NPS_APOP_A3_Poster_FINAL_v2.pdf

[49] http://www.nps.org.au/health_professionals/drug_use_evaluation_due_programs/due_kit_for_hospitals/apop/ educational_tools

1. For the potential for off-label use, including paediatric off-label use, the sponsor was requested to conduct routine pharmacovigilance and provide a separate analysis on this topic in each PSUR.
2. The sponsor should provide comment on the safety issues that led to increased restriction of this prescription in Brazil.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There is no requirement for a quality evaluation in a submission of this type.

Nonclinical

There is no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Efficacy

Acute pain in adults following surgery

Previously submitted efficacy data for acute pain consisted of a Phase I and ten Phase II trials. Nine of the trials addressed the treatment of acute pain in adults. There were two trials conducted in patients who had undergone dental surgery, six trials in patients who had undergone orthopaedic or general surgery, and one trial in patients with acute non-surgical pain. Two trials addressed treatment of primary dysmenorrhoea which has not been proposed in the current submission.

From those studies the ADEC considered that there was insufficient evidence of efficacy versus placebo for the acute pain indication. In particular, the withdrawal rate of patients from the single dose studies made it difficult to assess the efficacy of celecoxib over an entire dosage period. The Committee noted that single dose studies were not generally acceptable as evidence of therapeutic efficacy.

This submission included reports of a further ten studies and supportive published papers.

Study A3191086 examined efficacy of celecoxib for post-surgical pain relief. It was a prospective, multicentre, double-blind, double-dummy, randomised, active-controlled, parallel group study conducted in China in 2004. This study compared celecoxib with ibuprofen SR in the management of acute pain after orthopaedic or gynaecological surgery. Only two doses of either analgesic were given and patients continued to receive background analgesia. It was not clear if this was an equivalence study and what parameter was the primary measure of efficacy. This study also appeared underpowered to detect clinically significant differences between treatments and the effect of the additional analgesia may well have overshadowed any difference in effect of the two oral analgesics.

There were three published study reports from the 47 submitted that the clinical evaluator considered pivotal for post-surgical analgesia. These were randomised, double-blind, placebo-controlled trials that used the proposed celecoxib dose regimen and examined efficacy using an 11 point score for pain analysis. In the first study (Sun et al), 120 adults undergoing major plastic surgery were randomised to receive placebo, celecoxib 200 mg after surgery and then 200 mg bd for 3 days or celecoxib 400 mg 30 to 90 minutes prior to surgery, 200 mg after surgery then 200 mg bd for 3 days post surgery. Efficacy measures included pain scores and the need for rescue analgesics. Assessments were performed to Day 7 post-

surgery. The two groups given celecoxib had similar reductions in post-operative pain and similar requirements for opioid analgesics during the first 3 post-operative days. Opioid use in the first 3 post-operative days was significantly less in the post-operative and peri-operative celecoxib groups than in the placebo group with morphine equivalent usage 18 and 23 mg versus 68 mg on Day 1, 5 and 13 mg versus 40 mg on Day 2 and 3 and 3 mg versus 32 mg on Day 3 respectively ($p< 0.05$).

In the second pivotal paper (White et al 2007), 80 adult patients undergoing laparoscopic surgery were randomised to celecoxib or placebo, with celecoxib administered as an initial 400 mg dose in the recovery room then 200 mg bd for 3 additional days after surgery. Post-operative pain scores and the need for opioid-containing analgesics were recorded though the primary efficacy parameter was time to resume normal dietary, bowel and physical activities. The later two were statistically and clinically different, favouring celecoxib. "Rescue" analgesic medication at 24 hours, 48 hours and 72 hours after discharge was significantly reduced in the celecoxib group versus placebo (54% versus 90%, 39% versus 88% and 31% versus 84% on Days 1, 2 and 3 respectively). In the post-anaesthesia care unit, 32% of placebo treated patients vs. 36% given celecoxib required opioid analgesia, however the mean dose was lower for celecoxib patients at 84 µg versus 127 µg fentanyl given intravenously for the placebo group.

In the third study (Nikanne et al) 120 patients undergoing tonsillectomy were randomised to receive celecoxib (200 mg x 2), ketoprofen (100 mg x 2) or placebo pre-operatively and for 5 days and then prn. The primary efficacy measure was consumption of rescue analgesic during the first 24 hours after surgery. All patients received rescue oxycodone in the first 24 hours post-surgery with a mean of 5 doses in the celecoxib group, 5 in the ketoprofen group and 6 in the placebo group. Pain scores were assessed only to 24 hours and were similar in all groups.

On the basis of these three studies, in combination with the previously evaluated studies in post-operative analgesia, the clinical evaluator has recommended approval of celecoxib for post-surgical pain in adults. As the maximum duration of pain assessment was 7 days in the pivotal studies the evaluator has recommended that use for this indication be restricted to 7 days rather than 10 days as proposed by the sponsor.

Acute pain in adults following musculoskeletal and/or soft tissue injury

Five multicentre, double-blind, placebo-controlled, randomised parallel group studies comparing celecoxib at the proposed dose with ibuprofen, naproxen, diclofenac, ibuprofen and diclofenac slow release respectively in patients with acute ankle sprain showed celecoxib to be non-inferior to comparator NSAIDs. Patients were treated for up to 10 days. These studies were designed to determine equivalence with the primary efficacy criteria of Patient's Global Assessment of Injury and VAS pain scale at Day 4.

Two randomised, double-blind, double-dummy, parallel group studies considered pain in patients with acute tendonitis and/or bursitis of the shoulder.

Study 201 compared celecoxib (given as an initial 400 mg dose then 200 mg at least 8 hours later then 200 mg bd) with naproxen 500 mg bd and placebo. The primary efficacy variable was maximum pain intensity at rest on Day 14. Maximum pain intensity was measured on a VAS in which 0 = no pain and 100 was the most severe pain. The study was designed to show superiority over placebo rather than equivalence of celecoxib with naproxen. Ninety eight patients received celecoxib, 100 received naproxen and 108 received placebo and were eligible for the ITT analysis. At baseline mean (SD) maximum pain intensity at rest was 69.3 (13.77) for placebo, 70.4 (13.10) for celecoxib and 69.9 (14.99) for naproxen. At Day 14

mean maximum pain scores at rest were reduced by 25.8 in the placebo group, 34.5 in the celecoxib group and by 33.1 in the naproxen group. The comparison celecoxib versus placebo was statistically significant. The comparisons of naproxen versus placebo and celecoxib versus naproxen were not statistically significant.

Study 122 compared celecoxib 200 mg bd or naproxen 500 mg bd in patients with acute tendinitis and/or bursitis of the shoulder. Patients were treated for 14 days and followed for a further 2 weeks. There was no placebo arm and the study was designed to show equivalence with a between-group difference of 15 mm or greater in the VAS for maximum pain intensity at rest considered to be clinically significant. Paracetamol up to 3 g daily was used as rescue medication. The primary efficacy variable, as in study 201, was maximum pain intensity at rest at Day 14 measured on the same VAS. Ninety nine patients received celecoxib and 103 received naproxen and were eligible for the ITT analysis. At Day 14, mean maximum pain scores at rest had reduced by 47.9 for celecoxib and 42.3 for naproxen with 95% CI for difference (-12.52, 1.38), thus equivalence was demonstrated for the primary efficacy variable. Sixty (62.5%) patients given celecoxib and 55 (57.3%) patients given naproxen took rescue paracetamol with a mean of 0.7 tablets/day in both groups.

Acute lower back pain

Study 0164 was a multicentre, randomised, double-blind, double-dummy study comparing efficacy and safety of celecoxib 200 mg bd after an initial 400 mg dose with sodium diclofenac 75 mg bd in subjects with acute low back pain. The primary efficacy variable was change from baseline at Day 3 in patient-rated pain intensity on a VAS from 0 (no pain) to 100 mm (worst pain). The study was designed to show non-inferiority with 10 mm on the VAS considered a clinically significant difference. The primary analysis was the PP analysis which included 114 patients given celecoxib and 113 given ibuprofen. At Day 3 mean pain intensity had decreased from 76.8 to 36.3 in patients given celecoxib and from 76.3 to 33.0 in patients given diclofenac. Non-inferiority was examined using least mean squares (LMS). The LMS difference was -2.56 (95%CI -7.67, 2.56), thus non-inferiority was demonstrated. Non-inferiority was also demonstrated for the MITT population.

Another previously evaluated study in patients with low back pain was also described. This was a negative study comparing celecoxib with a slow release diclofenac product not registered in Australia.

Safety

No combined analysis of safety information from the short term studies previously submitted and/or contained in this submission was presented. No new safety issues were identified.

Celecoxib currently has indications for symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis with a recommended dose of 200 mg daily. Patients with rheumatoid arthritis may take up to 400 mg daily for short term management of flares or exacerbations. Extensive safety data for the 200 mg daily dose are available for the current indications with less data on the 200 mg bd dose. It is known that adverse events such as GI bleeding, increases in blood pressure and reduction in renal function are dose-related for NSAIDs including selective COX-2 inhibitors. The Product Information also advises that *as the CV risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used.*

The PI for Celebrex provides results for the following long term studies which included patients given celecoxib 200 mg bd:

- ADAPT (the Alzheimer's Disease Anti-inflammatory Prevention Trial). This study did not show a significantly increased cardiovascular risk with celecoxib 200 mg bd compared to placebo. The relative risk compared to placebo for a similar composite endpoint (CV death, myocardial infarction [MI], stroke) was 1.14 (95% CI 0.61 to 2.12) with celecoxib 200 mg bd. The incidence of MI was 1.1% (8/717 patients) with celecoxib 200 mg bd and 1.2% (13/1,070 patients) with placebo.
- APC trial (Adenoma Prevention with Celecoxib) and the PreSAP trial (Prevention of Spontaneous Adenomatous Polyps). In the APC trial, there was a dose related increase in the composite endpoint of CV death, MI, or stroke (adjudicated) with celecoxib compared to placebo over three years of treatment. The PreSAP trial did not demonstrate a statistically significant increased risk for the same composite endpoint.

In the APC trial, the hazard ratios compared to placebo for a composite endpoint of CV death, MI or stroke (adjudicated) were 3.4 (95% CI 1.4 to 8.5) with celecoxib 400 mg bd and 2.8 (95% CI 1.1 to 7.2) with celecoxib 200 mg bd. Cumulative rates for this composite endpoint over three years were 20/671 (3.0%), and 17/685 (2.5%), respectively, compared to 6/679 (0.9%) for placebo. The increases for both celecoxib dose groups versus placebo were mainly driven by MI. In the PreSAP trial, the hazard ratio compared to placebo for this same composite endpoint was 1.2 (95% CI 0.6 to 2.4) with celecoxib 400 mg once daily. Cumulative rates for this composite endpoint over three years were 21/933 (2.3%), compared to 12/628 (1.9%) for placebo.

Celecoxib, in common with all COX-2 inhibitors, is contraindicated for peri-operative treatment of pain in patients undergoing CABG surgery. This contraindication was instituted following studies showing an increase in adverse cardiovascular outcomes seen in patients given other COX-2 inhibitors (parecoxib, the parenteral pro-drug of valdecoxib, followed by oral valdecoxib) following CABG surgery. The increased risk of adverse cardiovascular outcomes seen in two studies of parecoxib/valdecoxib was 2.2% in one study and 3.4% in the other. No increased risk of adverse cardiovascular outcomes was seen in 1050 general surgical patients given either placebo or parecoxib/valdecoxib, however the event rate in that study was quite low with 17 (3.2%) cardiovascular events in the placebo group and 14 (2.7%) in the COX-2 group. The clinical evaluator has presented a more recent published integrated analysis in non-cardiac surgery patients given parecoxib/valdecoxib in the post-operative setting which also showed no increased risk of adverse cardiovascular outcomes.

The clinical evaluator identified another published paper which recommended that COX-2 inhibitors should also be avoided after procedures with an arterial anastomosis such as vascular surgery, free tissue transfer and solid organ transplantation. The basis for this recommendation is the postulation that endothelial prostacyclin appears to be synthesized primarily by inducible COX-2, thus selective COX-2 inhibitors preserve haemostasis but potentially at the expense of increased vascular occlusion. However, no evidence of increased risk in these patient groups was presented.

Risk Management Plan

The review of the Risk Management Plan by OMSM noted that the sponsor has identified no new safety concerns. The sponsor has proposed routine pharmacovigilance. The OMSM evaluator considered there may be an increase in off-label use, particularly paediatric off-label use and requested the sponsor provide a separate analysis on this topic in subsequent PSURs. The overall Risk Management Plan was considered acceptable.

Risk-Benefit Analysis

The data presented are sufficient to show that celecoxib at a dose of 200 mg bd provides clinically significant analgesia after surgery and for musculoskeletal/soft tissue pain. The sponsor has proposed a dose of 200 mg daily with 200 mg bd to be taken only if needed. While this is consistent with the current advice to use the minimum effective dose there is no evidence that 200 mg daily is a minimum effective dose. If any dose regimen is approved for acute pain it should be the regimen for which evidence of efficacy was presented.

The maximum duration of assessment for post-surgery acute pain was 7 days while the sponsor has proposed 10 days. Assessment of efficacy in patients with musculoskeletal/soft tissue pain showed consistent analgesic effect when compared with placebo and a range of active control NSAIDs given at appropriate doses for up to 14 days.

There are considerable data on the increased risk of adverse cardiovascular outcomes from 200 mg bd given longer term. There is very little information on the short term cardiovascular risk for 200 mg bd, however it would be lower than the risk of long term use.

The sponsor was requested to submit any additional information on cardiovascular safety of the 200 mg bd dose for short term use to 10 days.

Celecoxib currently can be taken at a dose of 200 mg bd for short term use in patients with rheumatoid arthritis who have disease flares or exacerbations and for primary dysmenorrhoea. The maximum recommended treatment duration for primary dysmenorrhoea is 5 days while no maximum duration is stated for rheumatoid arthritis.

The Delegate proposed to approve Celebrex (celecoxib) for treatment of acute pain in adults following surgery or musculoskeletal and/or soft tissue injury. The maximum recommended duration of treatment should be 5 days, unless the sponsor can provide satisfactory data on the cardiovascular safety of 200 mg bd doses for 10 days. The dose regimen should be a loading dose of 400 mg then 200 mg bd for up to 5 days. Should the sponsor wish to pursue a treatment duration of up to 10 days then safety data to show that there is no additional risk of adverse cardiovascular outcomes with the additional duration of use of this higher dose should be provided.

The advice of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) was requested particularly concerning:

- whether the requested 200 mg daily dose should be recommended for treatment of acute pain and whether the duration of use should be limited to 5 days as proposed;
- whether the dose recommendations for acute pain should include a statement that efficacy has been demonstrated only for the 200 mg bd dose.

Having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, the ACPM agreed with the Delegate's proposal and recommended the following indication:

Short-term treatment of acute pain in adults following surgery or musculoskeletal and/or soft tissue injury

In making this recommendation, the ACPM advised that evidence of the safety and efficacy of the formulation and the dosage regimen for the proposed new indication had been sufficiently demonstrated. However, as there is little evidence to conclude that cardiovascular risk is reduced in the context of a short five day course of treatment; the product and consumer information materials must highlight these risks as a contraindication. The ACPM supported the Delegate in setting a maximum recommended duration of treatment to be a loading dose of 400mg then 200mg once or twice daily as required for up to 5 days.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Celebrex (celecoxib) 100mg, 200mg and 400mg capsules (AUST R 67901, 67902 and 101341), indicated for:

"Short-term treatment of acute pain in adults following surgery or musculoskeletal and/or soft tissue injury"

Following extensive discussion with the Delegate, the PI and CMI were amended to the satisfaction of both the sponsor and the TGA to reflect the ACPM's advice regarding cardiovascular risk.

Attachment 1. Product Information

PRODUCT INFORMATION

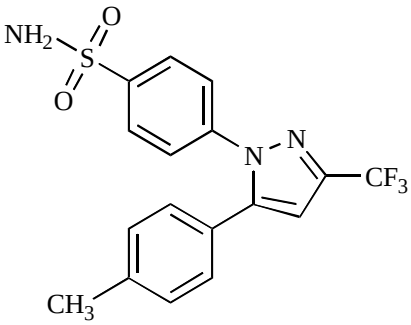
CELEBREX® 100 mg and CELEBREX 200 mg Capsules

Celecoxib 100 mg

Celecoxib 200 mg

DESCRIPTION

Celecoxib is a diaryl substituted pyrazole and has the following chemical structure and formula:



$C_{17}H_{14}F_3N_3O_2S$ M.W. = 381.38

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide

CAS registry no: 169590-42-5

100 mg Capsules: Opaque, white capsules with 2 blue bands marked 7767 and 100.

200 mg Capsules: Opaque, white capsules with 2 gold bands marked 7767 and 200.

Celecoxib is weakly acidic with a pKa in water of 11.1 and is practically insoluble in water. Celecoxib is chemically unrelated to anti-inflammatory agents of steroidal or non-steroidal nature. Celecoxib does not contain a chiral centre.

CELEBREX 100 mg and 200 mg capsules contain lactose, sodium lauryl sulfate, povidone, croscarmellose sodium, and magnesium stearate. The capsule shells contain gelatin, titanium dioxide and the inks contain: iron oxide yellow CI 77492 (200 mg capsule) and indigo carmine CI 73015 (100 mg capsule).

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: M01AH Coxibs

Celecoxib is a cyclooxygenase-2 (COX-2) specific inhibitor, a member of a larger class of non-steroidal anti-inflammatory drugs, that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily by inhibition of COX-2. At therapeutic concentrations in humans celecoxib does not inhibit cyclooxygenase-1 (COX-1). COX-2 is induced in response to inflammatory stimuli. This leads to the synthesis and accumulation of inflammatory prostanoids, in particular prostaglandin E2, causing inflammation, oedema and pain. In animal models, celecoxib acts as an anti-inflammatory, analgesic, and antipyretic agent by blocking the production of inflammatory prostanoids via COX-2 inhibition. In animal colon tumour models, celecoxib reduced the incidence and multiplicity of tumours.

In-vivo and *ex-vivo* studies show that celecoxib has a very low affinity for the constitutively expressed COX-1 enzyme. Consequently at therapeutic doses celecoxib has no effect on prostanoids synthesised by activation of COX-1 thereby not interfering with normal COX-1 related physiological processes in tissues, particularly the stomach, intestine and platelets.

Pharmacokinetics

Absorption

When celecoxib is given under fasting conditions, peak plasma concentrations are reached after approximately 2-3 hours. Intersubject variability in the Cmax and AUC is about 30%. Under fasting conditions, both peak plasma levels (Cmax) and area under the curve (AUC) are roughly dose proportional up to 200 mg BD; at higher doses there are less than proportional increases in Cmax and AUC (see Pharmacokinetics, Food Effects). Absolute bioavailability studies have not been conducted because of celecoxib's low solubility in aqueous media. The relative oral bioavailability of CELEBREX capsules compared with a suspension is about 99%. With multiple dosing, steady state conditions are reached on or before day 5.

Food Effects: When CELEBREX capsules were taken with a high fat meal, peak plasma levels were delayed for about 1 to 2 hours with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in Cmax and AUC, which is thought to be due to the low solubility of the drug in aqueous media. CELEBREX, at doses up to 200 mg BD can be administered without regard to the timing of meals. When multiple total daily doses of celecoxib as high as 1200 mg were given with food, an improved correlation between the dose and AUC (0-12) was observed.

Coadministration of CELEBREX with an aluminum- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in Cmax and 10% in AUC.

Distribution

In healthy subjects, celecoxib is highly protein bound (~97%) within the therapeutic dose range. *In-vitro* studies indicate that it binds primarily to albumin, and to a lesser extent, α_1 glycoprotein. The apparent volume of distribution at steady state is about 400 L in healthy young adults, suggesting extensive tissue distribution.

Metabolism

Celecoxib is extensively metabolised in the liver. *In-vitro* and *in-vivo* studies indicate that metabolism is mainly by cytochrome P450 CYP 2C9 (see Interactions with Other Medicines). Three metabolites have been identified in human plasma, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate. Pharmacological activity resides in the parent drug. The main metabolites found in human plasma have no detectable COX-1 or COX-2 inhibitory activity.

Cytochrome P450 2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP 2C9*3 polymorphism.

Patients who are known or suspected to be poor P450 2C9 metabolisers based on previous history should be administered CELEBREX with caution as they may have abnormally high plasma concentrations due to reduced metabolic clearance. Consider starting treatment at a reduced dose (see Dosage and Administration and Interactions with Other Medicines).

Elimination

Elimination of celecoxib is mostly by hepatic metabolism with less than 1% of the dose being excreted unchanged in the urine. Following a single oral dose of radiolabelled drug, approximately 57% of the dose was excreted in the faeces and 27% was excreted into the urine. The primary metabolite in both the urine and faeces was the carboxylic acid metabolite (73% of the dose) with low amounts of the glucuronide also appearing in the urine. At steady state the elimination half-life ($t_{1/2}$) was 4-15 hours and the clearance was about 500 mL/min. It appears that the low solubility of the drug prolongs absorption resulting in variable terminal half-life ($t_{1/2}$) determinations.

Special Populations

Hepatic Impairment: A pharmacokinetic study in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment has shown that steady state celecoxib AUC is increased about 40% and 180%, respectively, above that seen in healthy control subjects. Therefore, CELEBREX capsules should be introduced at half the recommended dose in arthritis patients with moderate hepatic impairment.

Patients with severe hepatic impairment have not been studied. Therefore, the use of CELEBREX in patients with severe hepatic impairment (Child-Pugh score ≥10) is contraindicated (see Contraindications and Dosage and Administration).

Renal Impairment: In elderly volunteers with age related reductions in glomerular filtration rate (GFR) (mean GFR>65mL/min/1.73m2) and in patients with chronic stable renal insufficiency (GFR 35-60mL/min/1.73m2) celecoxib pharmacokinetics were comparable to those seen in patients with normal renal function. No significant relationship was found between serum creatinine (or creatinine clearance) and celecoxib clearance. Severe renal insufficiency would not be expected to alter clearance of celecoxib since the main route of

elimination is via hepatic metabolism to inactive metabolites. There are no studies in patients with severe renal impairment.

Elderly Subjects: At steady state, subjects older than 65 years of age had a 40% higher Cmax and a 50% higher AUC than those of younger subjects. In elderly females, the Cmax and AUC were higher than those for elderly males predominantly due to the lower body weight of the females. No dosage adjustment in the elderly is generally necessary. However, for elderly patients with a body weight of less than 50kg treatment should be initiated at the lowest recommended dose.

Children: CELEBREX is not approved for use in patients under 18 years of age.

Race: Meta-analysis of pharmacokinetic studies has suggested an approximately 40% higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

CLINICAL TRIALS

Osteoarthritis (OA)

CELEBREX has demonstrated significant reduction in joint pain compared to placebo. CELEBREX was evaluated for treatment of the signs and the symptoms of OA of the knee and hip in approximately 4,200 patients in placebo- and active-controlled clinical trials of up to 12 weeks duration. In patients with OA, treatment with CELEBREX 100 mg BD or 200 mg once daily (OD) resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. In three 12-week studies of pain accompanying OA flare, CELEBREX doses of 100 mg BD and 200 mg BD provided significant reduction of pain within 24-48 hours of initiation of dosing. At doses of 100 mg BD or 200 mg BD the effectiveness of CELEBREX was shown to be similar to that of naproxen 500 mg BD. Doses of 200 mg BD provided no additional benefit above that seen with 100 mg BD. A total daily dose of 200 mg has been shown to be equally effective whether administered as 100 mg BD or 200 mg OD.

Rheumatoid Arthritis (RA)

CELEBREX has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. CELEBREX was evaluated for treatment of the signs and symptoms of RA in approximately 2,100 patients in placebo- and active-controlled clinical trials of up to 24 weeks in duration. CELEBREX was shown to be superior to placebo in these studies, using the ACR20 Responder Index, a composite of clinical, laboratory, and functional measures in RA. CELEBREX doses of 100 mg BD and 200 mg BD were similar in effectiveness and both were comparable to naproxen 500 mg BD.

Although CELEBREX 100 mg BD and 200 mg BD provided similar overall effectiveness, some patients derived additional benefit from the 200 mg BD dose. Doses of 400 mg BD provided no additional benefit above that seen with 100-200 mg BD.

Ankylosing Spondylitis (AS)

CELEBREX has been investigated in 896 patients in placebo and active (diclofenac, naproxen or ketoprofen) controlled clinical trials of 6 weeks (one trial) and 12 weeks (three trials) duration for the symptomatic treatment of AS. At doses of 100 mg twice daily (BD), 200 mg once daily (OD), and 400 mg once daily (OD), CELEBREX was statistically superior to placebo for all measures of efficacy including global pain intensity, global disease activity and functional impairment. In two 12 week studies of celecoxib at 200 mg total daily dose and 400 mg total daily dose, non- inferiority was demonstrated relative to diclofenac 150 mg total daily dose for global pain intensity. Results for global pain intensity are presented below.

Table 1: Global pain intensity[a] in CELEBREX ankylosing spondylitis clinical trials

Study	Placebo	Celecoxib 200 mg TDD[b]	Ketoprofen 100 mg BD	Naproxen 500 mg BD	Diclofenac 150 mg TDD[b]
Study 193	**N=156**	**N=137**	**--**	**N=157**	**--**
Baseline Mean	73.5	70.8	--	71.7	--
Mean Change, Week 12	-9.9	-30.0	--	-36.3	--
p-value versus placebo[c]	--	<0.001	--	<0.001	--
Study 137	**N=76**	**N=80**	**N=90**	**--**	**--**
Baseline Mean	69.5	70.4	65.7	--	--
Mean Change, Week 6	-11.9	-25.7	-22.5	--	--
p-value versus placebo[c]	--	0.0068	0.0512	--	--
Study 243	**--**	**N=126**	**--**	**--**	**N=123**
Baseline Mean	--	66.5	--	--	65.9
Mean Change, Week 12	--	-29.1	--	--	-32.7
[95% Confidence Interval][d]	--	[-33.6 to -24.6]	--	--	[-37.1 to -28.2]
Study 247	**--**	**N=107**	**--**	**--**	**N=115**
Baseline Mean	--	66.3	--	--	67.0
Mean Change, Week 12	--	-25.8	-	--	-28.2
[95% Confidence Interval][d]	--	[-31.1 to -20.6]	--	--	[-33.1 to 23.2]

[a] As measured using 100 mm Visual Analogue Scale. Values for mean change represent least squares mean changes from baseline to the end of treatment, with last observation carried forward for patients who withdrew prior to the end of treatment.

[b] TDD = Total daily dose: celecoxib 200 mg TDD was administered as 100 mg twice daily (Study 137) or 200 mg once daily (Studies 193, 243, and 247); diclofenac 150 mg TDD was administered as Sustained Release 75 mg twice daily in Study 243, or 50 mg three times daily in Study 247.

[c] Based on Analysis of Covariance models with the effects of treatment and centre, and baseline value as covariate.

[d] Based on Analysis of Covariance models; for Study 243, baseline values and age as covariates and treatment, gender and centres as factors; for Study 247, baseline value as a covariate and treatment and centres as factors. Although Study 247 did not reach its target for patient enrolment, a post-hoc analysis indicated that the statistical power of the study to detect treatment differences was not significantly weakened.

Dysmenorrhoea

The analgesic efficacy of celecoxib 400 mg for the treatment of primary dysmenorrhoea has been established in replicate, single dose, controlled studies where the primary measures of efficacy were Summed Pain Intensity Difference for the first 8 hours (SPID8) and the sum of the pain relief scores for the first 8 hours (TOTPAR8). A secondary measure of efficacy was Time to Onset of Analgesia. Naproxen sodium 550 mg was included in a third arm of these studies for comparison against placebo.

On the basis of the primary measures of efficacy, Studies 129 and 130 show that celecoxib is significantly superior to placebo in the treatment of primary dysmenorrhoea. In Study 129, the median Time to Onset of Analgesia for celecoxib was significantly shorter than that

observed for placebo. In Study 130, the median Time to Onset of Analgesia for celecoxib was shorter than that observed for placebo, but the difference was not significant.

Table 2: Analgesic efficacy of celecoxib for primary dysmenorrhoea

Study	SPID8	TOTPAR8	Median Time to Onset of Analgesia
	Mean [SD]	Mean [SD]	(hr:min)
129			
Placebo (N = 122)	6.0 [7.2]	12.8 [10.2]	01:05
Celecoxib 400 mg (N = 122)	10.1 [7.1]*	18.3 [10.2]*	00:52*
Naproxen sodium 550 mg (N = 122)	11.5 [6.4]*	20.6 [9.2]*	00.45*
130			
Placebo	6.4 [6.8]	13.0 [10.2]	01:27
Celecoxib 400 mg	9.6 [6.3]*	18.0 [9.5]*	00:53
Naproxen sodium 550 mg	11.7 [5.6]*	21.3 [7.8]*	00.50*

*Result is statistically significantly different from placebo ($p<0.05$)

Dental Surgery

The analgesic efficacy of CELEBREX was demonstrated in five studies of patients with post oral surgery pain, a well validated pain model. In these studies 1,130 patients were evaluated including over 360 at single doses of 100 mg or 200 mg. These doses showed analgesic activity beginning by 45 minutes and continuing for approximately 8 hours.

In the placebo controlled comparative study with aspirin (650 mg), celecoxib 100 mg provided statistically significant pain relief and reduction in pain intensity compared to placebo. Although time to onset of pain relief was 0.6 hours for aspirin and 1.0 hour for CELEBREX, a greater proportion of the CELEBREX group completed the study without rescue medication.

Four further single dose studies compared CELEBREX with placebo and either ibuprofen (400 mg) or naproxen sodium (550 mg). All active agents were statistically superior to placebo. Median time to onset of perceptible pain relief with CELEBREX 100 mg was 45 and 39 mins; CELEBREX 200 mg 38, 30, 44 and 40 mins; ibuprofen 33 and 28 mins, naproxen sodium 24 and 36 mins.

Post Surgery

The efficacy of CELEBREX for use in acute pain post surgery has been demonstrated in three pivotal studies; all were randomised, double blind and placebo controlled trials. Two of the studies had a duration of 3 days and the third study was for 5 days post-operative. All three studies used an 11 point score for pain analysis.

The first study was conducted in 120 patients undergoing major plastic surgery e.g. breast augmentation, abdominoplasty procedure. The patients received CELEBREX either as an initial 400mg post-operative dose, then 200mg BD for 3 days (40 patients) or 400mg 30-90mins before surgery then 200mg BD for 3 days; the remaining 40 patients received placebo. The primary variable 'opioid analgesia use' was significantly less in the post-operative and peri-operative groups compared to the placebo group for the 3 post-operative days (18 and 23mg vs. 68mg; 5 and 13mg vs. 40mg; 3 and 3mg vs. 32mg respectively, $p<0.05$) as were the

average pain scores. As a result, pain scores were relatively low with the greatest difference (approximately 1.75) being at 4h and 24h.

The second study was conducted in 77 patients undergoing laparoscopic surgery. The patients received either placebo (38) or 400mg/day CELEBREX (39) administered initially in the recovery room and then continued as 200mg BD for 3 days post-surgery. The primary variable was the times to resume normal dietary (3±2 vs. 2±2 days), bowel (3±2 vs. 2±1 days) and physical activities (6±3 vs. 4±2 days); these latter two were significantly and clinically different. The effects on pain management were assessed by pain score and rescue analgesia requirements. The pain scores on the first, second and third days were significantly lower in the celecoxib group vs. placebo (differences at 24, 48 and 72h = 2, 2 and 1). The corresponding percentages of patients requiring rescue analgesia were similarly significantly lower (21, 15, 12% vs. 30, 29, 27% at 24, 48 and 72h).

The third study was conducted to evaluate the management of pain after tonsillectomy. Thirty-nine patients received CELEBREX 200mg, 39 received placebo and 37 received ketoprofen 100mg. This was initially pre-operative and then BD for 5 days and then as required. The primary outcome parameter was the consumption of rescue analgesic during the first 24h after surgery. All patients in the CELEBREX group, 32 of 37 (86%) in the ketoprofen group (p=0.024, CELEBREX vs. ketoprofen) and 37 of 39 (95%) in the placebo group were provided oxycodone for rescue analgesia during the first 4h after surgery. In the CELEBREX group, the time to first dose of rescue analgesia was significantly shorter than in the ketoprofen group (p=0.039). All patients were provided rescue analgesia during the first 24h after surgery. The total number of oxycodone doses was 215 (mean 5 [range 2-14]) in the CELEBREX group, 179 (5[1-9]) doses in the ketoprofen group and 230 (6[1-13]) doses in the placebo patients (p=0.021, placebo vs. ketoprofen).

Musculoskeletal Pain

The efficacy of CELEBREX was demonstrated in five studies in patients with musculoskeletal pain, including ankle sprain and low back pain. In these studies over 1,822 patients were evaluated.

Four studies in ankle sprain demonstrated CELEBREX 200 mg BD to be non-inferior to a variety of active comparators (naproxen, ibuprofen or diclofenac) in the treatment of acute ankle sprains in all primary measures and in most secondary measures, with one instance of inferiority to the active comparator (Physician's Global Assessment of Ankle Injury, day 4).

Finally in a further study in low back pain, the CELEBREX treatment was observed to be as effective as diclofenac.

Celecoxib Long-term Arthritis Safety Study (CLASS)

Study Design

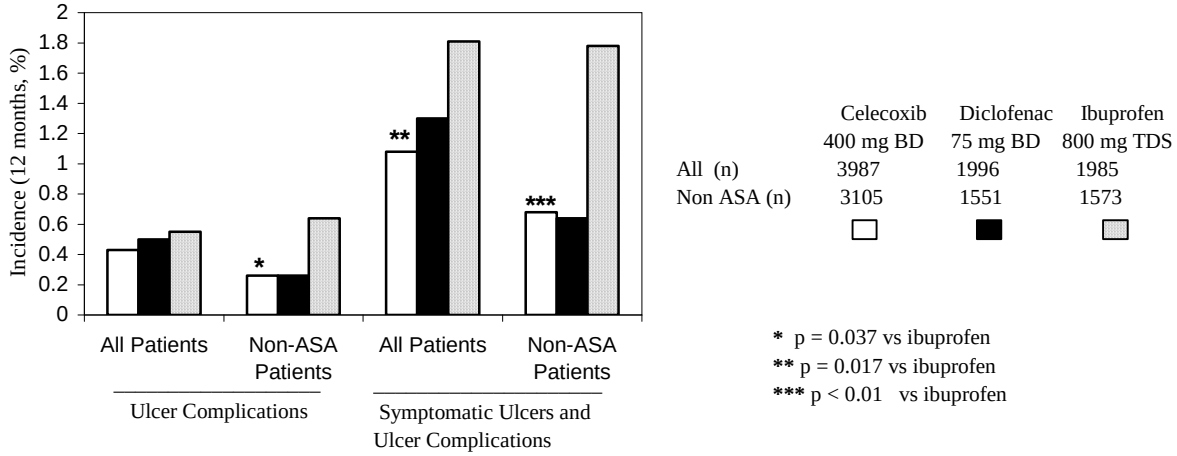
A prospective 12 month study was conducted in approximately 5,800 OA patients and 2,200 RA patients. The primary endpoint of this outcome study was the incidence of *complicated ulcers* (gastrointestinal bleeding, perforation or obstruction) in CELEBREX treated patients compared to each comparator. Patients received CELEBREX 400 mg BD (4-fold and 2-fold greater than the recommended OA and RA doses, respectively), ibuprofen 800 mg TDS (approved maintenance dose is 1600 mg daily) or diclofenac 75 mg BD

(approved maintenance dose is 75-100 mg daily) for a median exposure of 9 months for CELEBREX and diclofenac, and 6 months for ibuprofen. Patients were allowed to take concomitant low-dose aspirin ≤325 mg mostly for cardiovascular prophylaxis.

Study Results

No statistically significant differences were demonstrated for the incidence of complicated ulcers among the three treatment groups in all patients. In an additional non-protocol specified analysis, there was no difference in the incidence of *complicated and symptomatic ulcers* in patients on CELEBREX vs. those on diclofenac, although the incidence was significantly lower for CELEBREX than for ibuprofen in all patients, and in those patients not taking aspirin (ASA) (Figure 1). Approximately 22% of patients were taking low-dose aspirin. Concomitant low-dose aspirin use increased the risk of complicated and symptomatic ulcers on CELEBREX, diclofenac and ibuprofen (see Clinical Trials, Use with Aspirin). The incidence rates for diclofenac may be underestimated because of a higher incidence of early withdrawals due to GI adverse events than CELEBREX and ibuprofen.

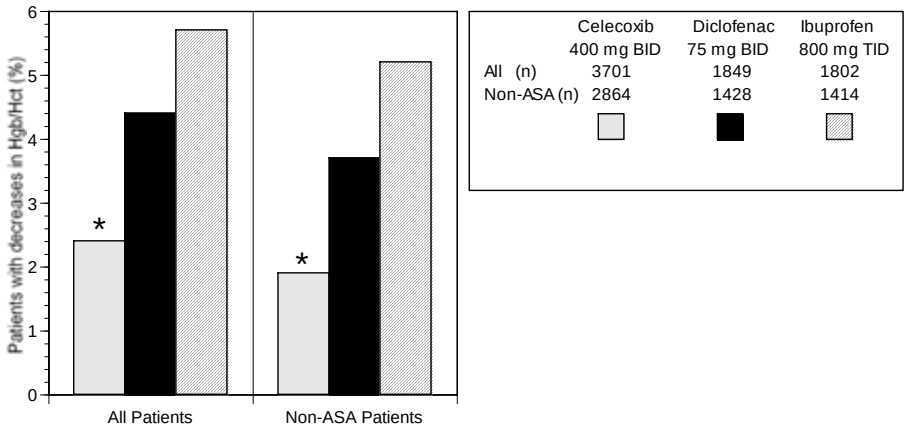
Figure 1: Incidence of symptomatic ulcers and ulcer complications



CELEBREX (4-fold and 2-fold greater than the recommended OA and RA doses, respectively) was also associated with a significantly lower incidence of clinically relevant decreases in haemoglobin (>20 g/L) or haematocrit (≥10 points) than ibuprofen and diclofenac regardless of aspirin use (Figure 2).

The incidence of clinically relevant decreases in haemoglobin and haematocrit in CELEBREX patients taking aspirin was lower than in ibuprofen and diclofenac patients taking aspirin.

Figure 2: Incidence of clinically relevant decreases in haemoglobin and/or haematocrit



*p<0.05 vs. ibuprofen and diclofenac

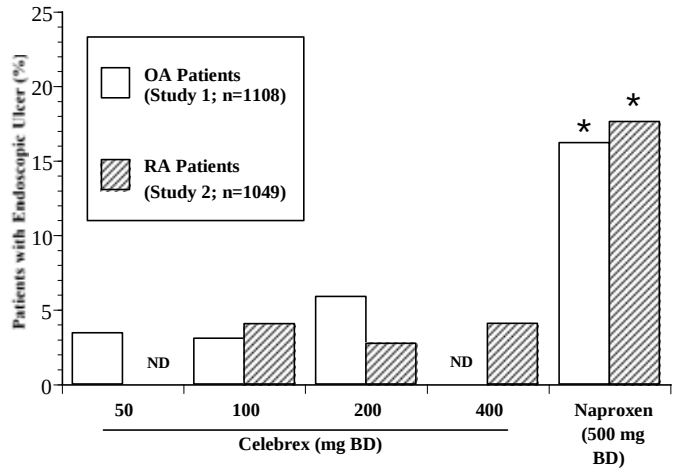
In the original registration studies, the incidence of serious upper gastrointestinal complications (bleeding, perforation, gastric outlet obstruction) with CELEBREX is not significantly different from placebo and is approximately 8-fold less than with non-specific COX inhibitors.

Endoscopic Studies

Scheduled upper GI endoscopic evaluations were performed in over 4,500 arthritis patients who were enrolled in five controlled randomised 12-24 week trials using active comparators, two of which also included placebo controls. Twelve-week endoscopic ulcer data are available on approximately 1,400 patients and 24 week endoscopic ulcer data are available on 184 patients on CELEBREX at doses ranging from 50-400 mg BD. In all three studies that included naproxen 500 mg BD, and in the study that included ibuprofen 800 mg TDS, CELEBREX was associated with a statistically significantly lower incidence of endoscopic ulcers over the study period. Two studies compared CELEBREX with diclofenac 75 mg BD; one study revealed a statistically significantly higher prevalence of endoscopic ulcers in the diclofenac group at the study endpoint (6 months on treatment), and one study revealed no statistically significant difference between cumulative endoscopic ulcer incidence rates in the diclofenac and CELEBREX groups after 1, 2, and 3 months of treatment. There was no consistent relationship between the incidence of gastroduodenal ulcers and the dose of CELEBREX over the range studied.

Figure 3 and Table 3 summarise the incidence of endoscopic ulcers in two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers.

Figure 3: Incidence of endoscopically observed gastroduodenal ulcers after twelve weeks of treatment



ND = Not Done

* Significantly different from all other treatments; p<0.05.

CELEBREX 100 mg BD, 200 mg once daily or 200 mg BD are the recommended doses.
These studies were not powered to compare the endoscopic ulcer rates of CELEBREX vs. placebo.
Study 1: placebo ulcer rate = 2.3%
Study 2: placebo ulcer rate = 2.0%

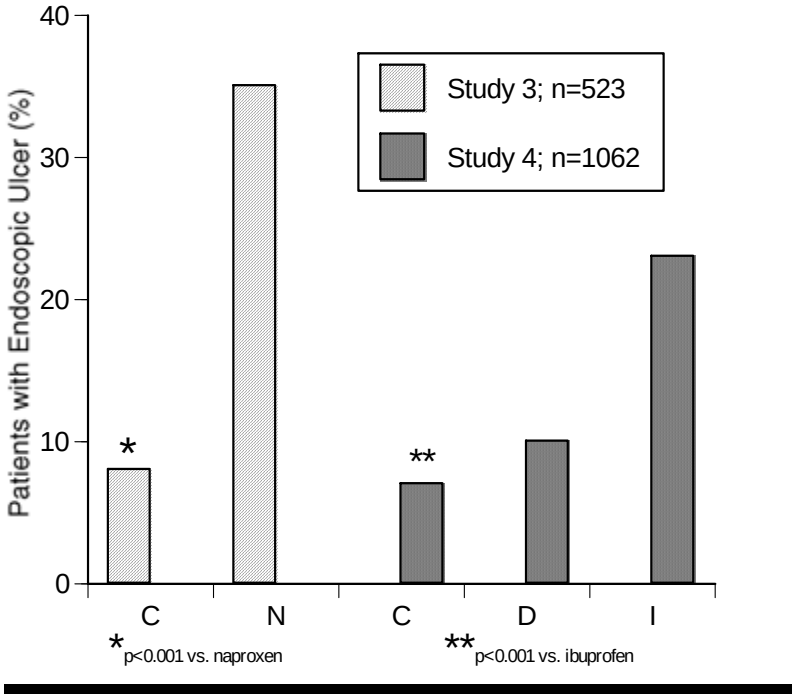
Table 3: Incidence of gastroduodenal ulcers from endoscopic studies in OA and RA patients

	3 Month Studies	
	Study 1 (n = 1108)	**Study 2 (n= 1049)**
Placebo	2.3% (5/217)	2.0% (4/200)
CELEBREX 50 mg BD	3.4% (8/233)	---
CELEBREX 100 mg BD	3.1% (7/227)	4.0% (9/223)
CELEBREX 200 mg BD	5.9% (13/221)	2.7% (6/219)
CELEBREX 400 mg BD	---	4.1% (8/197)
Naproxen 500 mg BD	16.2% (34/210)*	17.6% (37/210)*

*p≤ 0.05 vs. all other treatments

Figure 4 and Table 4 summarise data from two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers. Patients underwent interval endoscopies every 4 weeks to give information on ulcer risk over time.

Figure 4: Cumulative incidence of gastroduodenal ulcers based on 4 serial endoscopies over 12 weeks



C = CELEBREX 200 mg BD
N = Naproxen 500 mg BD
D = Diclofenac 75 mg BD
I = Ibuprofen 800 mg TDS

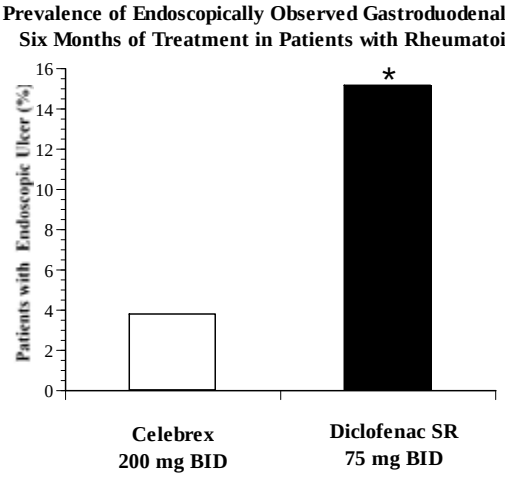
Table 4: Incidence of gastroduodenal ulcers from 3-month serial endoscopy studies in OA and RA patients

	Week 4	**Week 8**	**Week 12**	**Final**
Study 3 (n=523)				
CELEBREX 200 mg BD	4.0% (10/252)*	2.2% (5/227)*	1.5% (3/196)*	7.5% (20/266)*
Naproxen 500 mg BD	19.0% (47/247)	14.2% (26/182)	9.9% (14/141)	34.6% (89/257)
Study 4 (n=1062)				
CELEBREX 200 mg BD	3.9% (13/337)†	2.4% (7/296)†	1.8%(5/274)†	7.0% (25/356)†
Diclofenac 75 mg BD	5.1% (18/350)	3.3% (10/306)	2.9%(8/278)	9.7% (36/372)
Ibuprofen 800 mg TDS	13.0% (42/323)	6.2% (15/241)	9.6% (21/219)	23.3% (78/334)

* p≤ 0.05 CELEBREX vs. naproxen based on interval and cumulative analyses
† p≤ 0.05 CELEBREX vs. ibuprofen based on interval and cumulative analyses

One randomised and double-blinded 6-month study in 430 RA patients was conducted in which an endoscopic examination was performed at 6 months. The results are shown in Figure 5.

Figure 5:



* Significantly different from Celebrex; p<0.001

The correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established.

Serious clinically significant upper GI bleeding has been observed in patients receiving CELEBREX in controlled and open labelled trials, albeit infrequently. Patients most at risk of developing an ulcer complication were the elderly (≥75 years), patients in poor health or with cardiovascular disease, aspirin users and patients with a history of a GI ulcer or upper GI bleeding.

Use with Aspirin

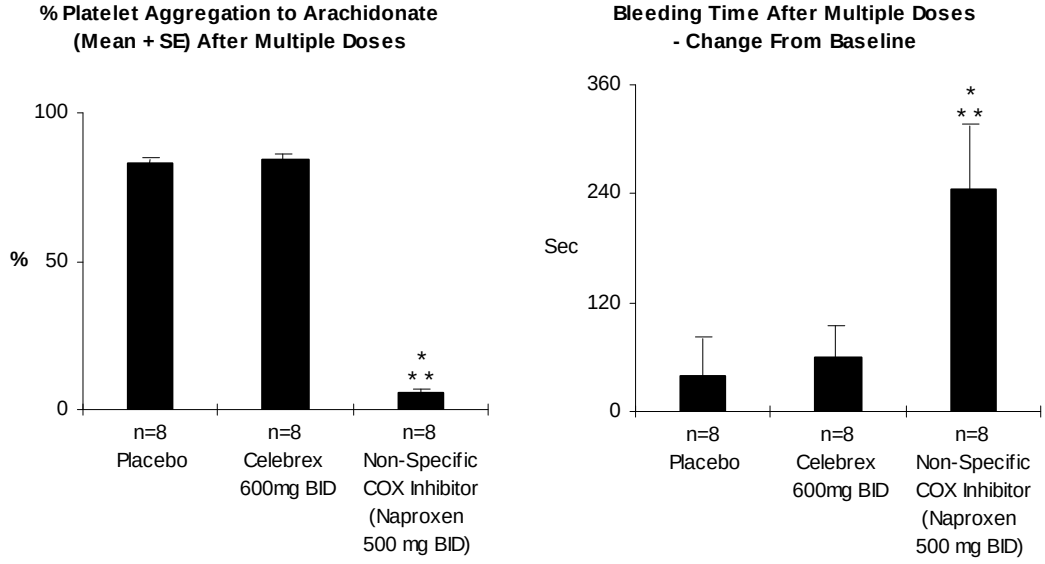
Approximately 11% of patients (440/4,000) enrolled in 4 of the 5 endoscopic studies were taking aspirin (≤325 mg/day). In the CELEBREX groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than the endoscopic ulcer rates observed in the active comparator groups, with or without aspirin.

In the Celecoxib Long-term Arthritis Safety Study, approximately 22% of patients were taking aspirin (≤325 mg/day). Subjects on concomitant low-dose aspirin experienced 4-fold higher rates of *complicated and symptomatic ulcers* on CELEBREX.

Platelet Function

In healthy volunteers, CELEBREX, at multiple doses of 600 mg BD (three times the highest recommended therapeutic dose) had no effect on platelet aggregation and bleeding time compared to placebo. Active controls (non-specific COX inhibitors i.e. naproxen, diclofenac, ibuprofen) all significantly reduced platelet aggregation and prolonged bleeding time.

Figure 6:



* Significantly different from placebo; $p<0.05$

** Significantly different from CELEBREX; $p<0.05$

Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis.

Cardiovascular Safety – Long-term Studies Involving Patients with Sporadic Adenomatous Polyps

Two studies involving patients with sporadic adenomatous polyps were conducted with celecoxib i.e., the APC trial (Adenoma Prevention with Celecoxib) and the PreSAP trial (Prevention of Spontaneous Adenomatous Polyps). In the APC trial, there was a dose-related increase in the composite endpoint of cardiovascular death, myocardial infarction, or stroke (adjudicated) with celecoxib compared to placebo over 3 years of treatment. The PreSAP trial did not demonstrate a statistically significant increased risk for the same composite endpoint.

In the APC trial, the hazard ratios compared to placebo for a composite endpoint of cardiovascular death, myocardial infarction, or stroke (adjudicated) were 3.4 (95% CI 1.4-8.5) with celecoxib 400 mg twice daily and 2.8 (95% CI 1.1-7.2) with celecoxib 200 mg twice daily (cumulative rates for this composite endpoint over 3 years were 20/671 subjects, 3.0%, and 17/685 subjects, 2.5%, respectively, compared to 6/679 subjects, 0.9%, for placebo). The increases for both celecoxib dose groups versus placebo were mainly driven by myocardial infarction.

In the PreSAP trial, the hazard ratio compared to placebo for this same composite endpoint was 1.2 (95% CI 0.6-2.4) with celecoxib 400 mg once daily (cumulative rates for this composite endpoint over 3 years were 21/933 subjects, 2.3%, compared to 12/628 subjects, 1.9%, for placebo).

When data from the APC and PreSAP trials were considered together, risk for cardiovascular thromboembolic events was greater in celecoxib-treated patients with a history of atherosclerotic cardiovascular disease, than in celecoxib-treated patients without such history.

Cardiovascular Safety – Long-term Study of Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)

Data from a third long-term study, ADAPT (The Alzheimer's Disease Anti-inflammatory Prevention Trial), did not show a significantly increased cardiovascular risk with celecoxib 200 mg BD compared to placebo. The relative risk compared to placebo for a similar composite endpoint (CV death, MI, stroke) was 1.14 (95% CI 0.61 – 2.12) with celecoxib 200 mg twice daily. The incidence of myocardial infarction was 1.1% (8/717 patients) with celecoxib 200 mg twice daily and 1.2% (13/1070 patients) with placebo.

Cardiovascular Safety – Celecoxib Long-term Arthritis Safety Study (CLASS)

Cardiovascular safety outcomes were evaluated in CLASS (see Clinical Trials for description of trial). Kaplan-Meier cumulative rates for investigator reported serious cardiovascular thromboembolic adverse events (including MI, pulmonary embolism, deep venous thrombosis, unstable angina, transient ischaemic attacks and ischaemic cerebrovascular accidents) demonstrated no differences between the celecoxib, diclofenac or ibuprofen treatment groups. The cumulative rates in all patients at nine months for celecoxib, diclofenac and ibuprofen were 1.2%. 1.4% and 1.1%, respectively. The cumulative rates in non-aspirin users at nine months in each of the three treatment groups were less than 1%. The cumulative rates for myocardial infarction in the non-aspirin users at nine months in each of the three treatment groups were less than 0.2%. There was no placebo group in the CLASS trial, which limits the ability to determine whether the three drugs tested had no increased risk of CV events or if they all increased risk to a similar degree.

Two large, controlled, clinical trials of a different COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see Contraindications).

INDICATIONS

For the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

For the treatment of primary dysmenorrhoea in adults.

**For the short-term treatment of acute pain in adults following surgery or musculoskeletal and/or soft tissue injury.

CONTRAINDICATIONS

Known hypersensitivity to celecoxib or any of the excipients contained in the CELEBREX capsules (see Description).

Demonstrated allergic-type reactions to sulfonamides.

CELEBREX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other non-steroidal anti-inflammatory drugs, including other COX-2 specific inhibitors. Severe, rarely fatal, anaphylactoid reactions to

non-steroidal anti-inflammatory drugs have been reported in such patients (see Precautions, Anaphylactoid Reactions).

CELEBREX should not be used with other non-steroidal anti-inflammatory drugs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

CELEBREX is contraindicated for the peri-operative treatment of pain in patients undergoing coronary artery bypass graft (CABG) surgery (see Precautions).

CELEBREX is contraindicated in:

- Patients with unstable ischaemic heart disease of thrombus aetiology or significant established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see Precautions, Cardiovascular and Thrombotic Events).
- Patients with active peptic ulceration or gastrointestinal (GI) bleeding.
- Patients with estimated creatinine clearance <30 mL/min.
- Patients with congestive heart failure (NYHA II-IV).
- Patients with severe hepatic impairment (Child-Pugh[#] score ≥10; see Pharmacology and Dosage and Administration).

[#] Child-Pugh is a classification of the severity of liver disease.

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (seconds over control)	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grade1-2	Grade3-4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one- and two-year patient survival: grade A - 100 and 85 percent; grade B - 80 and 60 percent; and grade C - 45 and 35 percent.

PRECAUTIONS

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks and benefits of therapy (see Contraindications and Precautions).

Cardiovascular and Thrombotic Events

COX-2 inhibitors have been associated with an increased risk of cardiovascular and thrombotic adverse events. Celecoxib is a COX-2 inhibitor (see Clinical Trials, Cardiovascular Safety).

All NSAIDs, both COX-2 selective and non-selective may cause an increased risk of serious cardiovascular thrombotic events. This risk may increase with duration of use.

Patients with known cardiovascular disease, history of atherosclerotic cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

CELEBREX should be used with caution in patients at high risk of cardiovascular disease including those with significant *and multiple* risk factors (e.g. diabetes, hypertension, hypercholesterolaemia, cardiac failure and smokers).

To minimize the potential risk for an adverse cardiovascular event in patients treated with celecoxib, the lowest effective dose should be used for the shortest duration possible (see Clinical Trials, Cardiovascular Safety and Dosage and Administration).

Physicians and patients should remain alert for such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

Gastrointestinal Effects

Infrequently, serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach or intestine has been observed in patients treated with CELEBREX. Physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms.

CELEBREX (celecoxib) exhibited a low incidence of gastroduodenal ulceration and serious clinically significant GI events within clinical trials. The following information for non-steroidal anti-inflammatory drugs should be borne in mind.

Serious GI toxicity, such as bleeding, ulceration and perforation of the stomach, small intestine or large intestine can occur at any time, with or without warning symptoms, in patients treated with non-steroidal anti-inflammatory drugs. Minor upper GI problems, such as dyspepsia, are common, and may also occur at any time during NSAID therapy. Therefore, physicians should remain alert for ulceration and bleeding in patients treated with non-steroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

Among 5,285 patients who received CELEBREX in the original arthritis trials of 1 to 6 months duration (most were 3 month studies) at a daily dose of 200 mg or more, 2 (0.04%) experienced significant upper GI bleeding, at 14 and 22 days after initiation of dosing. Approximately 40% of these 5,285 patients were in studies that required them to be free of ulcers by endoscopy at study entry. Thus it is unclear if this study population is representative of the general population.

The incidences of *complicated* and *symptomatic ulcers* for patients treated with CELEBREX 400 mg BD (4-fold and 2-fold greater than the recommended OA and RA doses, respectively) from the prospective randomised controlled long-term outcomes trial in 8000 OA and RA patients in which low dose aspirin use was allowed was 0.68% on CELEBREX alone and 1.08% on CELEBREX with or without aspirin.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. To minimise the potential risk of an ulcer complication, the lowest effective dose of CELEBREX should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors.

There is no definitive evidence that the concomitant administration of histamine H2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of CELEBREX when and if these adverse reactions appear.

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to CELEBREX. In post-marketing experience, rare cases of anaphylactoid reactions and angioedema have been reported in patients receiving CELEBREX. CELEBREX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see Contraindications and Precautions, Pre-existing Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Serious Skin Reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of celecoxib. Patients appear to be at highest risk for these events early in the course of therapy: the onset of the event occurring in the majority of cases within the first month of treatment. Celecoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Hypertension

As with all NSAIDs, celecoxib can lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. NSAIDs, including celecoxib, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of therapy with celecoxib and throughout the course of therapy.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a

compensatory role in the maintenance of renal perfusion. In these patients, administration of a non-steroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Such patients should be carefully monitored while receiving treatment with celecoxib. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors (see Precautions, Concomitant use of ACE Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics), and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with CELEBREX have shown renal effects similar to those observed with comparator NSAIDs.

At the present time the relative roles of COX-1 and COX-2 in renal physiology is incompletely understood. Celecoxib reduces the urinary excretion of PGE_2 and 6-keto-$PGF_{1\propto}$ (a prostacyclin metabolite) but leaves serum thromboxane B_2 (TXB_2) and urinary excretion of 11-dehydro-TXB_2, a thromboxane metabolite (both COX-1 products) unaffected.

Caution should be used when initiating treatment with CELEBREX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with CELEBREX.

No information is available regarding the use of CELEBREX in patients with advanced kidney disease. Therefore, treatment with CELEBREX is not recommended in these patients. If CELEBREX therapy must be initiated, close monitoring of the patient's kidney function is advisable.

Concomitant use of ACE Inhibitors or Angiotensin Receptor Antagonists and Anti-inflammatory Drugs and Thiazide Diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), and an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time, increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Concomitant use of all three classes of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the initiation of the treatment. The concomitant use of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Use with Other NSAIDs

The concomitant use of celecoxib and a non-aspirin NSAID should be avoided.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice, fatal fulminant hepatitis, liver necrosis, hepatic failure (some with fatal outcome), and liver transplant have been reported with NSAIDs, including CELEBREX (see Adverse Effects). In

controlled clinical trials of CELEBREX, the incidence of borderline elevations of liver tests was 6% for CELEBREX and 5% for placebo, and approximately 0.2% of patients taking CELEBREX and 0.3% of patients taking placebo had notable elevations of ALT and AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with CELEBREX. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), CELEBREX should be discontinued.

The incidence of elevations in ALT and/or AST may be increased in patients treated with celecoxib at doses greater than 400 mg daily.

Haematological Effects

Anaemia is sometimes seen in patients receiving CELEBREX. In controlled clinical trials the incidence of anaemia was 0.6% with CELEBREX and 0.4% with placebo. Patients on long-term treatment with CELEBREX should have their haemoglobin or haematocrit checked if they exhibit any signs or symptoms of anaemia or blood loss. CELEBREX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not appear to inhibit platelet aggregation at indicated dosages (see Clinical Trials, Celecoxib Long-term Arthritis Safety Study and Clinical Trials, Platelet Function).

Pre-existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other non-steroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, CELEBREX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Fluid Retention and Oedema

Fluid retention and oedema have been observed in some patients taking CELEBREX (see Adverse Effects). Therefore, CELEBREX should be used with caution in patients with fluid retention, hypertension, heart failure, compromised cardiac function, pre-existing oedema or other conditions predisposing to, or worsened by, fluid retention including those taking diuretic treatment or otherwise at risk of hypovolaemia. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

Use in Patients being Treated with Corticosteroids

Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

Use in Patients with Inflammatory Bowel Disease (IBD)

Short-term exposure of celecoxib to patients with ulcerative colitis (UC) in remission has not shown an exacerbation of IBD in spondyloarthropathies, but the implications of longer term exposure remain unknown. NSAIDs have been associated with an exacerbation of IBD associated with spondyloarthropathies.

Detecting Infections

By reducing inflammation, celecoxib may diminish the utility of diagnostic signs, such as fever, in detecting infections.

Carcinogenicity/Mutagenicity

Celecoxib was not carcinogenic in 2-year studies in rats given oral doses up to 200 mg/kg/day for males and 10 mg/kg/day for females (approximately 2-4 fold the human exposure as measured by the $AUC_{0\text{-}24\ h}$ at 400 mg BD, which is twice the recommended maximum daily dose), or in mice given dietary doses up to 25 mg/kg/day for males and 50 mg/kg/day for females (slightly less than human exposure at 400 mg BD).

Celecoxib was not mutagenic in an Ames test and a mutation assay in Chinese hamster ovary (CHO) cells, nor clastogenic in a chromosome aberration assay in CHO cells and an *in-vivo* micronucleus test in rat bone marrow.

Impairment of Fertility

Celecoxib did not affect male or female fertility in rats at oral doses up to 600 mg/kg/day (approximately 7-fold human exposure based on $AUC_{0\text{-}24\ h}$ at 400 mg BD, which is twice the recommended maximum daily dose).

Use in Pregnancy: Pregnancy Category B3

There is no information on the use of celecoxib in pregnant women. CELEBREX use is not recommended in pregnancy unless it is considered clinically essential (see information on animal studies). No studies have been done to evaluate the effect of celecoxib on the closure of the ductus arteriosus in humans. In animal studies, both COX-1 and COX-2 have been shown to be present in the ductus arteriosus of fetal lambs and to contribute to maintenance of patency. Therefore, use of CELEBREX during the third trimester of pregnancy should be avoided, and CELEBREX should not be used during the first and second trimesters of pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus. The effects of CELEBREX on labour and delivery in pregnant women are not known.

In rats, celecoxib caused early embryonic death at doses greater than 30 mg/kg/day administered before mating and during early gestation (approximately 2-fold human exposure based on $AUC_{0\text{-}24\ h}$ at 400 mg BD, which is twice the recommended maximum daily dose). This effect is attributable to inhibition of prostaglandin production, and is not associated with permanent alteration of reproductive function. Celecoxib was shown to cross the placenta in rats. Teratology studies disclosed an increased incidence of wavy ribs in one study in rats dosed at 100 mg/kg/day, increased incidences of diaphragmatic hernias at 30 and 100 mg/kg/day in another rat study; and increased incidences of rib and sternebral abnormalities in rabbits at doses of 60 mg/kg/day or greater and cardiovascular abnormalities

in rabbits at doses of 150 mg/kg/day or greater. At the no-effect dose in rats (10 mg/kg/day), $AUC_{0\text{-}24\ h}$ was similar to that in humans dosed at 400 mg BD. At the threshold dose of 60 mg/kg/day in rabbits, $AUC_{0\text{-}24\ h}$ was slightly below that in humans dosed at 400 mg BD. Celecoxib had a marginal effect on parturition in rats, causing slight prolongation of gestation and parturition and increased incidence of still births at oral doses of 10 mg/kg/day or greater (slightly greater than human exposure based on $AUC_{0\text{-}24\ h}$ at 400 mg BD).

Use in Lactation

Studies in rats show that celecoxib is excreted in milk at concentrations similar to those in plasma. Administration of celecoxib to lactating women has shown very low transfer of celecoxib into breast milk. Because of the potential for adverse reactions to celecoxib in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the expected benefit of the drug to the mother.

Effects on Ability to Drive and Use Machines

The effect of CELEBREX on ability to drive or use machinery has not been studied, but based on its pharmacodynamic properties and overall safety profile it is unlikely to have an effect.

Use in the Elderly

Of the total number of patients who received CELEBREX in clinical trials, more than 3,300 were 65-74 years of age, while approximately 1,300 additional patients were 75 years and over. While the incidence of adverse experiences tended to be higher in elderly patients, no substantial differences in safety and effectiveness were observed between these subjects and younger subjects. Other reported clinical experience including data from the Celecoxib Long-term Arthritis Safety Study have not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see Precautions, Gastrointestinal Effects).

In clinical studies comparing renal function as measured by the GFR, BUN (Blood Urea Nitrogen) and creatinine, and platelet function as measured by bleeding time and platelet aggregation, the results were not different between elderly and young volunteers.

Use in Children

CELEBREX is not approved for use in patients under 18 years of age.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. In controlled clinical trials elevated BUN occurred more frequently in patients receiving CELEBREX compared with patients on placebo. This abnormality was also seen in patients who received comparator NSAIDs in these studies. The clinical significance of this abnormality has not been established.

Interactions with Other Medicines

General

Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Patients who are known or suspected to be poor CYP 2C9 metabolisers based on previous history/experience with other CYP 2C9 substrates should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance. Co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. Consider starting treatment at a reduced dose (see Dosage and Administration).

In-vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an *in-vivo* drug interaction with drugs that are metabolised by P450 2D6.

ACE-inhibitors and Angiotensin II Antagonists

Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors and/or angiotensin II antagonists. This interaction should be given consideration in patients taking CELEBREX concomitantly with ACE-inhibitors and/or angiotensin II antagonists.

Frusemide

Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of frusemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Aspirin

CELEBREX can be used with low dose aspirin. However, concomitant administration of aspirin with CELEBREX may result in an increased rate of GI ulceration or other complications, compared to use of CELEBREX alone (see Clinical Trials, Celecoxib Long-term Arthritis Safety Study).

In the long-term outcome study, the incidences of MI, stroke, unstable angina and deep thrombophlebitis in non-aspirin users were 0.2%, <0.1%, <0.1% and 0.3% respectively and in aspirin users were 1.5%, 0.6%, 0.9% and 0.3% respectively. Incidence rates with CELEBREX were not different from those of the two comparators. Because of its lack of platelet effects, CELEBREX is not a substitute for aspirin for cardiovascular prophylaxis.

Fluconazole

Concomitant administration of fluconazole at 200 mg once daily resulted in a two-fold increase in celecoxib plasma concentration. This increase is due to the inhibition of celecoxib metabolism via P450 2C9 by fluconazole (see Pharmacokinetics, Metabolism). CELEBREX should be introduced at the lowest recommended dose in patients receiving fluconazole.

Lithium

In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BD with CELEBREX 200 mg BD as

compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when CELEBREX is introduced or withdrawn.

Oral Hypoglycaemics

The effect of celecoxib on the pharmacokinetics and/or pharmacodynamics of glibenclamide and tolbutamide has been studied and clinically important interactions have not been found.

Glucocorticoids

Oral glucocorticoids should be used with caution since they increase the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

Antacids

Coadministration of CELEBREX with an aluminium- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in Cmax and 10% in AUC.

Methotrexate

CELEBREX did not have a significant effect on the pharmacokinetics of methotrexate.

Ketoconazole

CELEBREX did not have a significant effect on the pharmacokinetics of ketoconazole.

Phenytoin

CELEBREX did not have a significant effect on the pharmacokinetics of phenytoin.

Warfarin

Anticoagulant activity should be monitored, particularly in the first few days, after initiating or changing CELEBREX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. The effect of celecoxib on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of 2 mg to 5 mg of warfarin. In these subjects, celecoxib did not alter the anticoagulant effect of warfarin as determined by prothrombin time. However, in post-marketing experience, bleeding events have been reported, *some of them fatal*, predominantly in the elderly, in association with increases in prothrombin time in patients receiving CELEBREX concurrently with warfarin (see Precautions, Gastrointestinal Effects).

Other Drug Interactions

No drug interaction data are available for CELEBREX and the co-administration of the following products: paracetamol, alcohol, aminoglycosides, bone marrow depressants, butemide, cholestyramine, colchicine, corticosteroids, cyclosporine, digoxin, gold compounds, indapamide, insulin, nephrotoxic agents, non-steroidal anti-inflammatory agents, oral contraceptives, potassium supplements, probenecid, valproic acid, zidovudine.

ADVERSE EFFECTS

Of the CELEBREX treated patients in controlled trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and over 1,000 were patients with post-surgical pain. More than 8,500 patients have received a total daily dose of CELEBREX of 200 mg (100 mg BD or 200 mg once daily) or more, including more than 400 treated at 800 mg (400 mg BD). Approximately 3,900 patients have received CELEBREX at these doses for 6 months or more; approximately 2,300 of these have received it for 1 year or more and 124 of these have received it for 2 years or more.

Adverse Events from Original CELEBREX Arthritis Trials

Table 5 lists all adverse events, regardless of causality, occurring in ≥2% of patients receiving CELEBREX from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or an active control group.

Table 5: Adverse events occurring in ≥ 2% of CELEBREX patients from original CELEBREX arthritis trials

	CELEBREX (100-200 mg BD or 200 mg once daily) (N=4146)	Placebo (N=1864)	Naproxen 500 mg BD (N=1366)	Diclofenac 75 mg BD (N=387)	Ibuprofen 800 mg TDS (N=345)
Gastrointestinal					
Abdominal pain	4.1%	2.8%	7.7%	9.0%	9.0%
Diarrhoea	5.6%	3.8%	5.3%	9.3%	5.8%
Dyspepsia	8.8%	6.2%	12.2%	10.9%	12.8%
Flatulence	2.2%	1.0%	3.6%	4.1%	3.5%
Nausea	3.5%	4.2%	6.0%	3.4%	6.7%
Body as a whole					
Back Pain	2.8%	3.6%	2.2%	2.6%	0.9%
Peripheral oedema	2.1%	1.1%	2.1%	1.0%	3.5%
Injury-accidental	2.9%	2.3%	3.0%	2.6%	3.2%
Central and peripheral nervous system					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
Psychiatric					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
Respiratory					
Pharyngitis	2.3%	1.1%	1.7%	1.6%	2.6%
Rhinitis	2.0%	1.3%	2.4%	2.3%	0.6%
Sinusitis	5.0%	4.3%	4.0%	5.4%	5.8%
Upper respiratory tract infection	8.1%	6.7%	9.9%	9.8%	9.9%
Skin					
Rash	2.2%	2.1%	2.1%	1.3%	1.2%

In placebo- or active-controlled clinical trials, the discontinuation rate due to adverse events was 7.1% for patients receiving CELEBREX and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the CELEBREX treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of CELEBREX patients, respectively). Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

The adverse event profile from the Celecoxib Long-term Arthritis Safety Study (at 4- and 2-fold the recommended doses for OA and RA, respectively) was similar to those reported in the arthritis controlled trials.

The following adverse events occurred in 0.1 - 1.9% of patients taking CELEBREX 100-200 mg BD or 200 mg once daily regardless of causality.

Gastrointestinal:	Constipation, diverticulitis, dysphagia, eructation, oesophagitis, gastritis, gastroenteritis, gastroesophageal reflux, haemorrhoids, hiatal hernia, melaena, dry mouth, stomatitis, tenesmus, tooth disorder, vomiting
Cardiovascular:	Aggravated hypertension, angina pectoris, coronary artery disorder, myocardial infarction, arrhythmia
General:	Allergy aggravated, allergic reaction, asthenia, chest pain, cyst, oedema generalised, face oedema, fatigue, fever, hot flushes, influenza-like symptoms, pain, peripheral pain
Resistance mechanism disorders:	Herpes simplex, herpes zoster, infection bacterial, infection fungal, infection soft tissue, infection viral, moniliasis, moniliasis genital, otitis media
Central, peripheral nervous system:	Leg cramps, hypertonia, hypoaesthesia, migraine, neuralgia, neuropathy, paraesthesia, vertigo
Female reproductive:	Breast fibroadenosis, breast neoplasm, breast pain, dysmenorrhoea, menstrual disorder, vaginal haemorrhage, vaginitis
Male reproductive:	Prostatic disorder
Hearing and vestibular:	Deafness, ear abnormality, earache, tinnitus
Heart rate and rhythm:	Palpitation, tachycardia
Liver and biliary system:	Hepatic function abnormal, AST increased, ALT increased
Metabolic and nutritional:	BUN increased, CPK increased, diabetes mellitus, hypercholesterolaemia, hyperglycaemia, hypokalaemia, nonprotein nitrogen increase, creatinine increased, alkaline phosphatase increase, weight increase
Musculoskeletal:	Arthralgia, arthrosis, bone disorder, fracture accidental, myalgia, neck stiffness, synovitis, tendinitis
Platelets (bleeding or clotting):	Ecchymosis, epistaxis, thrombocythaemia

Psychiatric:	Anorexia, anxiety, appetite increased, depression, nervousness, somnolence
Haemic:	Anaemia
Respiratory:	Bronchitis**,** bronchospasm, bronchospasm aggravated, coughing, dyspnoea, laryngitis, pneumonia
Skin and appendages:	Alopecia, dermatitis, nail disorder, photosensitivity reaction, pruritus, rash erythematous, rash maculopapular, skin disorder, skin dry, sweating increased, urticaria
Application site disorders:	Cellulitis, dermatitis contact, injection site reaction, skin nodule
Special senses:	Taste perversion
Urinary system:	Albuminuria, cystitis, dysuria, haematuria, micturition frequency, renal calculus, urinary incontinence, urinary tract infection
Vision:	Blurred vision, cataract, conjunctivitis, eye pain, glaucoma

Other Serious Adverse Events which Occur Rarely (<0.1%), Regardless of Causality

The following serious adverse events have occurred rarely in patients, taking CELEBREX. Cases reported only in post-marketing experience are indicated in italics.

Cardiovascular:	Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, *vasculitis, cerebral haemorrhage*
Gastrointestinal:	Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, oesophageal perforation, pancreatitis, ileus, ulcers (oesophageal, gastric and duodenal)
Liver and biliary systems:	Cholelithiasis, *hepatitis, fulminant hepatitis, jaundice, liver failure, liver necrosis, liver transplant, elevation of hepatic enzymes*
Haemic and lymphatic:	Thrombocytopenia, *agranulocytosis, aplastic anaemia, pancytopenia, leukopenia*
Metabolic:	*Hypoglycaemia*
Psychiatric:	*Hallucinations*

Nervous system:	Aseptic meningitis, ataxia, suicide, aggravated epilepsy, confusion, *ageusia*, *anosmia*
Renal:	Acute renal failure, *interstitial nephritis, hyponatraemia*
Reproductive System & Breast Disorders:	*Menstrual disorders*
Skin:	*Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis*
Ear:	Decreased hearing
Eye:	*Conjunctivitis*
General:	Sepsis, sudden death, *anaphylactoid reaction, angioedema, bullous eruption.*

Adverse Events from the Primary Dysmenorrhoea Studies

These studies had an overall incidence of adverse events of 30.5% in the placebo treatment period, 31.2% in the celecoxib treatment period, and 36.3% in the NSAID comparator (naproxen sodium) period. Overall, nausea, headache, and dizziness were the most common adverse events in the celecoxib treatment group. These adverse events can be related to primary dysmenorrhoea.

Adverse Events from Polyp Prevention Trials

The following additional adverse events* in Table 6 were reported at incidence rates greater than placebo in long-term polyp prevention studies of duration up to 3 years at daily doses from 400 mg up to 800 mg (see Clinical Trials, Cardiovascular Safety, Long-term Studies Involving Patients With Sporadic Adenomatous Polyps). Adverse events are listed by system organ class are ranked by frequency. Frequencies are defined as: very common (>10%), common (>1% and <10%), uncommon (>0.1% and <1%).

Table 6: Adverse reactions occurring in CELEBREX patients from long-term studies involving patients with sporadic adenomatous polyps

System Organ Class Frequency	**Adverse Drug Event**
Infections and infestations Common Uncommon	 Ear infection, fungal infection (primarily non-systemic) Helicobacter infection, herpes zoster, erysipelas, wound infection, gingival infection, labyrinthitis, bacterial infection
Neoplasms benign, malignant, and unspecified Uncommon	 Lipoma

System Organ Class Frequency	Adverse Drug Event
Psychiatric disorders Uncommon	Sleep disorder
Nervous system disorders Uncommon	Cerebral infarction
Eye disorders Uncommon	Vitreous floaters, conjunctival haemorrhage
Ear and labyrinth disorders Uncommon	Hypoacusis
Cardiac disorders Common Uncommon	Angina pectoris, myocardial infarction Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertrophy
Vascular disorders Very Common Uncommon	Hypertension* Deep vein thrombosis, haematoma
Respiratory, thoracic, and mediastinal disorders Common Uncommon	Dyspnoea Dysphonia
Gastrointestinal disorders Very Common Common Uncommon	Diarrhoea* Nausea, gastro-oesophageal reflux disease, diverticulum, vomiting*, dysphagia, irritable bowel syndrome Haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, stomatitis
Hepatobiliary disorders Rare	Elevation of hepatic enzymes
Skin and subcutaneous tissue disorders Uncommon	Dermatitis allergic
Musculoskeletal and connective tissue disorders Common Uncommon	Muscle spasms Ganglion
Renal and urinary disorders Common Uncommon	Nephrolithiasis Nocturia
Reproductive system and breast disorders Common Uncommon	Benign prostatic hyperplasia, prostatitis Vaginal haemorrhage, breast tenderness, dysmenorrhoea, ovarian cyst, menopausal symptoms
General disorders and administration site conditions Uncommon	Oedema

System Organ Class Frequency	Adverse Drug Event
Investigations Common Uncommon	 Blood creatinine increased, prostatic specific antigen increased, weight increased Blood potassium increased, blood sodium increased, blood testosterone decreased, haematocrit decreased, haemoglobin increased
Injury, poisoning and procedural complications Uncommon	 Foot fracture, lower limb fracture, epicondylitis, tendon rupture, fracture

*Hypertension, vomiting and diarrhoea are included in Table 6 because they were reported more frequently in these studies, which were of 3-year duration, compared to Table 5, which includes adverse events from studies of 12-week duration.

Other Adverse Effects

Intestinal anastomotic ulceration was observed in 3 of 58 patients enrolled in familial adenomatous polyposis clinical trials and who had prior intestinal surgery, one at 100 mg BD, and two at 400 mg BD.

DOSAGE AND ADMINISTRATION

As the cardiovascular risks of celecoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used (see Clinical Trials).

Patients on long-term treatment should be reviewed regularly, such as every three months, with regards to efficacy, risk factors and ongoing need for treatment.

Adults

The doses can be given without regard to timing of meals.

Osteoarthritis

The usual recommended daily dose is 200 mg taken once daily or in two divided doses.

Rheumatoid Arthritis

The recommended daily dose is 200 mg taken in two divided doses.

A dose of up to 400 mg daily may be used for short-term management of disease flares or exacerbations.

Ankylosing Spondylitis

The maximum recommended daily dose is 200 mg taken once daily or in two divided doses.

Primary Dysmenorrhoea

The recommended dose is 400 mg as a single dose or divided on the first day, followed by 200 mg once daily on subsequent days. Patients may be instructed to take an additional dose of 200 mg on any given day, if needed. The maximum recommended treatment duration is 5 days.

Acute Pain Following Surgery or Musculoskeletal and/or Soft Tissue Injury**

The recommended dose is a loading dose of 400mg then 200mg once or twice daily as required for up to 5 days.

The effective dose in this patient population is 200mg twice daily.

Elderly

No dosage adjustment is generally necessary. However, for elderly patients with a lower than average body weight (<50 kg), it is advisable to initiate therapy at the lowest recommended dose.

Hepatic Impairment

No dosage adjustment is necessary in patients with mild hepatic impairment. In arthritis patients with moderate hepatic impairment, CELEBREX should be introduced at half the recommended dose.

There is no clinical experience in patients with severe hepatic impairment. Therefore, the use of CELEBREX in patients with severe hepatic impairment (Child-Pugh score ≥10) is contraindicated (see Pharmacology and Contraindications).

Renal Impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment. There is no clinical experience in patients with severe renal impairment (see Pharmacokinetics).

Children

CELEBREX is not approved for use in patients under 18 years of age.

CYP 2C9 Poor Metabolisers

Patients who are known, or suspected to be CYP 2C9 poor metabolisers based on previous history/experience with other CYP 2C9 substrates should be administered celecoxib with caution. Consider starting treatment at a reduced dose (see Interactions With Other Medicines and Pharmacokinetics).

OVERDOSAGE

Clinical experience of overdose is limited. No overdoses of CELEBREX were reported during clinical trials. Doses up to 2400 mg/day for up to 10 days in 12 patients did not result in serious toxicity.

Symptoms following acute NSAID overdoses are usually limited to lethargy, drowsiness, nausea, vomiting, epigastric pain and other gastrointestinal adverse effects, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

There are no specific antidotes. Patients should be managed by symptomatic and supportive care following an overdose. Monitor patients for signs and symptoms of gastrointestinal ulceration and/or haemorrhage. Monitor serum electrolytes, renal function and urinalysis after significant overdose.

Consider activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within one or two hours of ingestion and may reduce absorption of the drug. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

No information is available regarding the removal of celecoxib by haemodialysis, but based on its high degree of plasma protein binding (>97%) dialysis is unlikely to be useful in overdose. Forced diuresis, alkalinisation of urine, haemodialysis, or haemoperfusion may not be useful due to high protein binding.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION

CELEBREX (celecoxib) 100 mg capsules are available in cartons of 60.

CELEBREX (celecoxib) 200 mg capsules are available in cartons of 10 or 30.

NAME AND ADDRESS OF THE SPONSOR

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DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 23 June 2010.

** Please note changes in the Product Information

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