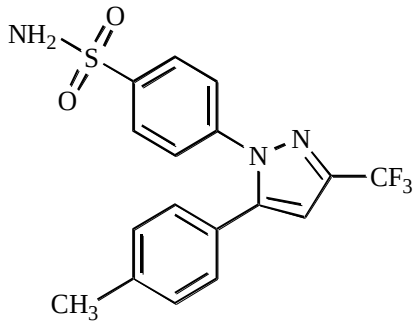
# PRODUCT INFORMATION
## KUDEQ® (celecoxib)

## NAME OF THE MEDICINE

KUDEQ (celecoxib) 100 mg and 200 mg capsules.

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



| | |
|---|---|
| Chemical name | 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide |
| Molecular formula: | $C_{17}H_{14}F_3N_3O_2S$ |
| Molecular weight | 381.38 |
| CAS Registry Number: | 169590-42-5. |

## DESCRIPTION

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.

KUDEQ 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); 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 (NSAIDs) 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 $C_{max}$ and AUC is about 30%. Under fasting conditions, both peak plasma levels ($C_{max}$) 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 $C_{max}$ 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 celecoxib capsules compared with a suspension is about 99%. With multiple dosing, steady state conditions are reached on or before day 5.

### *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, $\alpha_1$ 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 KUDEQ 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.

### *Food Effects*

When celecoxib 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 $C_{max}$ and AUC, which is thought to be due to the low solubility of the drug in aqueous media. Celecoxib, 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 celecoxib with an aluminium- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in $C_{max}$ and 10% in AUC.

### *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, KUDEQ 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 KUDEQ 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 >65 mL/min/1.73 $m^2$) and in patients with chronic stable renal insufficiency (GFR 35-60 mL/min/1.73 $m^2$) 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 (>65 years)*

At steady state, subjects older than 65 years of age had a 40% higher $C_{max}$ and a 50% higher AUC than those of younger subjects. In elderly females, the $C_{max}$ 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 50 kg treatment should be initiated at the lowest recommended dose.

*Children and Adolescents*

KUDEQ 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)

Celecoxib has demonstrated significant reduction in joint pain compared to placebo. Celecoxib 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 celecoxib 100 mg BD or 200 mg once daily 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, celecoxib doses of 100 mg BD or 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 efficacy of celecoxib 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)

Celecoxib has demonstrated a significant reduction in joint tenderness/pain and joint swelling compared to placebo. Celecoxib 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. Celecoxib was shown to be superior to placebo in these studies, using the American College of Rheumatology 20 (ACR20) Responder Index, a composite of clinical, laboratory, and functional measures in RA. Celecoxib doses of 100 mg BD and 200 mg BD were similar in efficacy and both were comparable to naproxen 500 mg BD.

Although celecoxib 100 mg BD and 200 mg BD provided similar overall efficacy, 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 mg - 200 mg BD.

## Ankylosing Spondylitis (AS)

Celecoxib has been investigated in 896 patients in placebo and active-controlled (diclofenac, naproxen or ketoprofen) 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), celecoxib 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 celecoxib 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 celecoxib 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 celecoxib, a greater proportion of the celecoxib group completed the study without rescue medication.

Four further single dose studies compared celecoxib 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 celecoxib 100 mg was 45 and 39 mins; celecoxib 200 mg 38, 30, 44 and 40 mins; ibuprofen 33 and 28 mins, naproxen sodium 24 and 36 mins.

**Post-Surgery**

The efficacy of celecoxib 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 celecoxib either as an initial 400 mg post-operative dose, then 200 mg BD for 3 days (40 patients) or 400 mg 30-90 mins before surgery then 200 mg 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 mg and 23 mg vs. 68 mg; 5 mg and 13 mg vs. 40 mg; 3 mg and 3 mg vs. 32 mg 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 4 h and 24 h.

The second study was conducted in 77 patients undergoing laparoscopic surgery. The patients received either placebo (38) or 400 mg/day celecoxib (39) administered initially in the recovery room and then continued as 200 mg BD for 3 days post-surgery. The primary variable was the times to resume normal dietary (3±2 days vs. 2±2 days), bowel (3±2 days vs. 2±1 days) and physical activities (6±3 days 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 h, 48 h and 72 h = 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 72 h).

The third study was conducted to evaluate the management of pain after tonsillectomy. Thirty-nine patients received celecoxib 200 mg, 39 received placebo and 37 received ketoprofen 100 mg. 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 24 h after surgery. All patients in the celecoxib group, 32 of 37 (86%) in the ketoprofen group (p=0.024, celecoxib vs. ketoprofen) and 37 of 39 (95%) in the placebo group were provided oxycodone for rescue analgesia during the first 4 h after surgery. In the celecoxib 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 24 h 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 patients (p=0.021, placebo vs. ketoprofen).

**Musculoskeletal Pain**

The efficacy of celecoxib 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 celecoxib 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 celecoxib treatment was observed to be as effective as diclofenac.

**Celecoxib Long-term Arthritis Safety Study (CLASS)**

***Study Design***

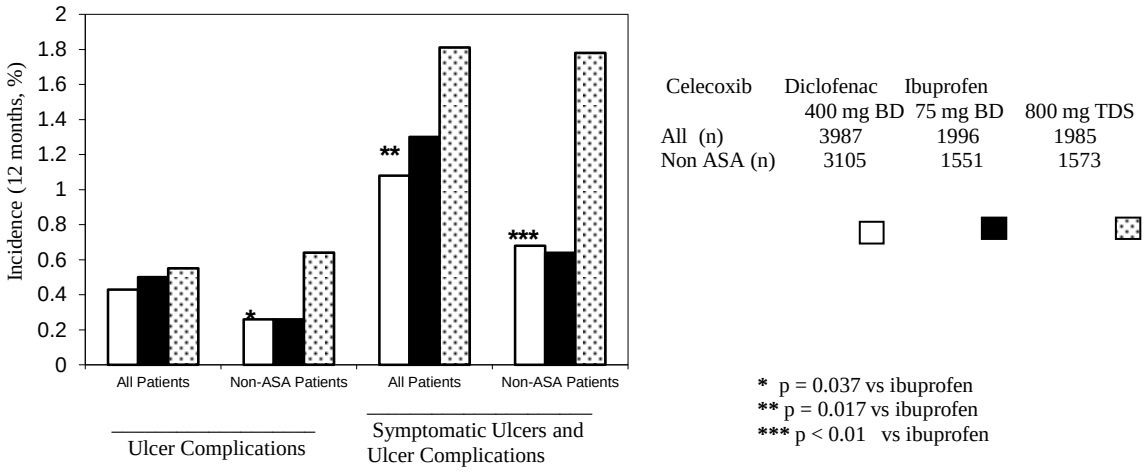
A prospective 12 month study was conducted in approximately 5,800 OA patients and 2,200 RA patients. The primary endpoint of this outcome study was the incidence of *complicated ulcers* (gastrointestinal bleeding, perforation or obstruction) in celecoxib treated patients compared to each comparator. Patients received celecoxib 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 celecoxib 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 celecoxib vs. those on diclofenac, although the incidence was significantly lower for celecoxib 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 celecoxib, 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 celecoxib and ibuprofen.

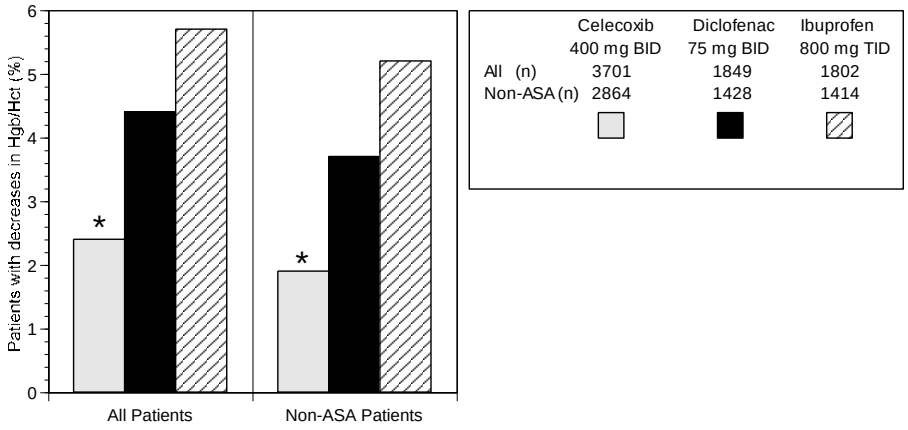
**Figure 1: Incidence of symptomatic ulcers and ulcer complications**




Celecoxib (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 celecoxib 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 celecoxib vs ibuprofen and diclofenac.

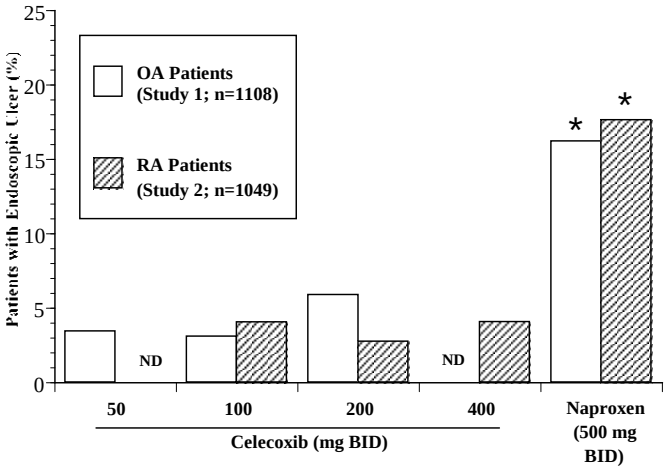
In the original registration studies, the incidence of serious upper gastrointestinal complications (bleeding, perforation, gastric outlet obstruction) with celecoxib is not significantly different from placebo and is approximately 8-fold less than with non-specific COX inhibitors.

## 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 celecoxib 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, celecoxib was associated with a statistically significantly lower incidence of endoscopic ulcers over the study period. Two studies compared celecoxib 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 celecoxib groups after 1, 2, and 3 months of treatment. There was no consistent relationship between the incidence of gastroduodenal ulcers and the dose of celecoxib 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.

Celecoxib 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 celecoxib vs. placebo.
Study 1: placebo ulcer rate = 2.3%.
Study 2: placebo ulcer rate = 2.0%.

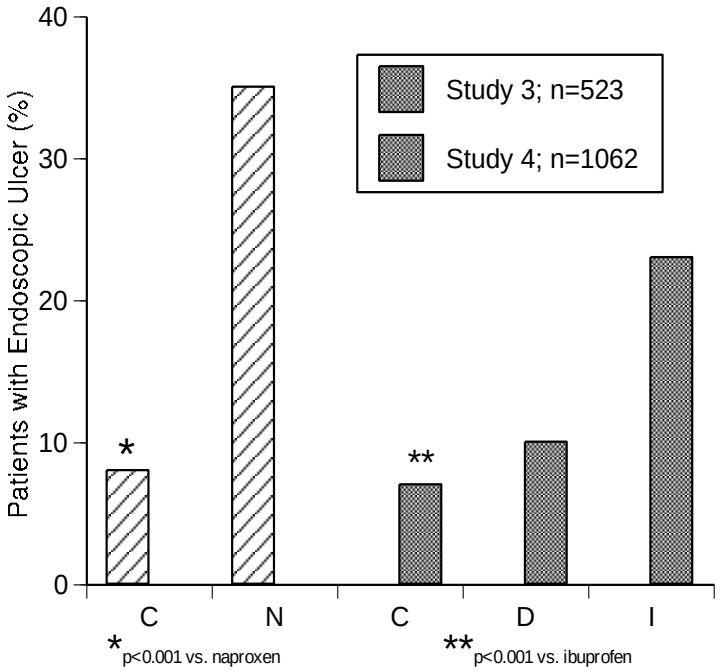
**Table 3: Incidence of gastroduodenal ulcers from endoscopic studies in OA and RA patients**

| | **3 Month Studies** | |
|---|---|---|
| | **Study 1 (n = 1108)** | **Study 2 (n= 1049)** |
| | | |
| Placebo | 2.3% (5/217) | 2.0% (4/200) |
| Celecoxib 50 mg BD | 3.4% (8/233) | --- |
| Celecoxib 100 mg BD | 3.1% (7/227) | 4.0% (9/223) |
| Celecoxib 200 mg BD | 5.9% (13/221) | 2.7% (6/219) |
| Celecoxib 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 = Celecoxib 200 mg BD
N = Naproxen 500 mg BD
D = Diclofenac 75 mg BD
I = Ibuprofen 800 mg TDS

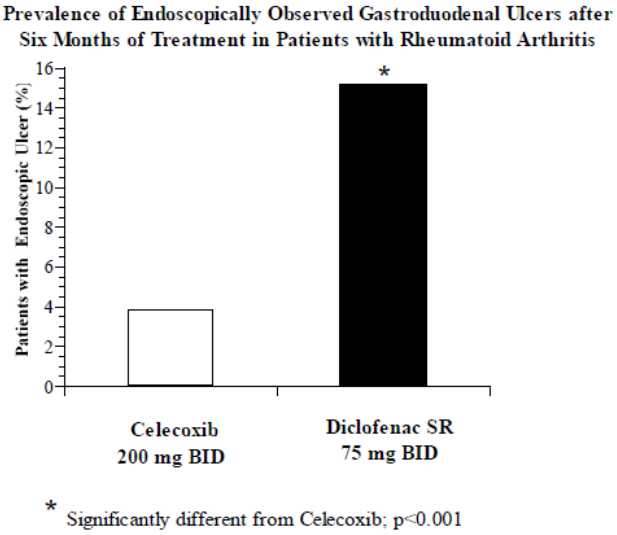
**Table 4: Incidence of gastroduodenal ulcers from 3-month serial endoscopy studies in OA and RA patients**

| | **Week 4** | **Week 8** | **Week 12** | **Final** |
|---|---|---|---|---|
| **Study 3 (n=523)** | | | | |
| Celecoxib 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)** | | | | |
| Celecoxib 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 celecoxib vs. naproxen based on interval and cumulative analyses.
†p≤ 0.05 celecoxib 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**




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 celecoxib 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

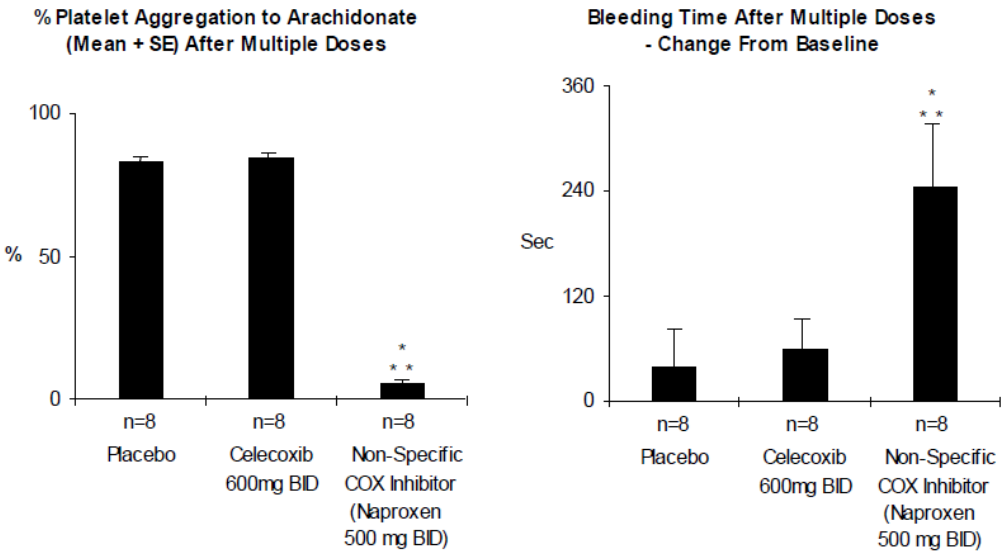
Approximately 11% of patients (440/4,000) enrolled in 4 of the 5 endoscopic studies were taking aspirin (≤325 mg/day). In the celecoxib groups, the endoscopic ulcer rate appeared to be higher in aspirin users than in non-users. However, the increased rate of ulcers in these aspirin users was less than 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 celecoxib.

### Platelet Function

In healthy volunteers, celecoxib, 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 (see Figure 6.

**Figure 6: Effects of celecoxib on platelet aggregation and bleeding time**




* Significantly different from placebo; $p<0.05$

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

Because of its lack of platelet effects, celecoxib 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 3.0% (20/671) and 2.5% (17/685) for the 200 mg twice daily and 400 mg twice daily celecoxib treatment groups, respectively, compared to 0.9% (6/679) for the placebo group. 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 rate for this composite endpoint over 3 years was 2.3% (21/933), compared to 1.9% (12/628) for the placebo group.

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 the ADAPT 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, 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 KUDEQ capsules (see DESCRIPTION).

Demonstrated allergic-type reactions to sulfonamides.

KUDEQ should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs, including other COX-2 specific

inhibitors. Severe, rarely fatal, anaphylactoid reactions to NSAIDs have been reported in such patients (see PRECAUTIONS, Anaphylactoid Reactions).

KUDEQ should not be used with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

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

KUDEQ 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 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 | Grade 1-2 | Grade 3-4 |

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 Thrombotic Events

COX-2 inhibitors, including celecoxib, have been associated with an increased risk of serious cardiovascular thrombotic adverse events, myocardial infarction, and stroke, which can be fatal (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, a medical history of cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

KUDEQ 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 minimise 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 symptoms of serious cardiovascular toxicity and the steps to take if they occur.

**Gastrointestinal Effects**

Infrequently, serious gastrointestinal (GI) toxicity such as bleeding, ulceration, and upper and lower GI perforation (including perforations of the stomach or intestine) has been observed in patients treated with celecoxib.

Celecoxib exhibited a low incidence of gastroduodenal ulceration and serious clinically significant GI events within clinical trials. The following information for NSAIDs 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 NSAIDs. 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 NSAIDs, 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.

Among 5,285 patients who received celecoxib 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 celecoxib 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 celecoxib alone and 1.08% on celecoxib with or without aspirin.

Patients most at risk of developing GI complications with NSAIDs are elderly patients; patients with cardiovascular disease; patients using concomitant aspirin or corticosteroids; patients who consume alcohol; or patients with a prior history of GI disease (such as ulceration, GI bleeding or inflammatory conditions). KUDEQ should be prescribed with extreme caution in these patients. Physicians and patients should remain alert for ulceration and GI bleeding, even in the absence of symptoms.

Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimise the potential risk of an ulcer complication, the lowest effective dose of KUDEQ 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 GI 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 GI side effects or allow the continuation of celecoxib 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 celecoxib. In post-marketing experience, rare cases of anaphylactoid reactions and angioedema have been reported in patients receiving celecoxib. KUDEQ 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 NSAID 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, Use with ACE Inhibitors, Angiotensin Receptor Antagonists, 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 celecoxib have shown renal effects similar to those observed with comparator NSAIDs. The relative roles of COX-1 and COX-2 in renal physiology are not completely understood. Celecoxib reduces the urinary excretion of $PGE_2$ and 6-keto-$PGF_{1\alpha}$ (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 KUDEQ in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with KUDEQ.

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

**Use with ACE Inhibitors, Angiotensin Receptor Antagonists, 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 Oral Anticoagulants**

The concomitant use of NSAIDs with oral anticoagulants increases the risk of bleeding and should be given with caution (see INTERACTIONS WITH OTHER MEDICINES, Oral Anticoagulants).

**Use with Drugs Metabolised by CYP2D6**

Celecoxib has shown to be a moderately potent CYP2D6 inhibitor. For drugs that are metabolised by CYP2D6, a dose reduction during initiation of celecoxib treatment or a dose

increase upon termination of celecoxib treatment may be necessary (see INTERACTIONS WITH OTHER MEDICINES, Dextromethorphan and Metoprolol).

**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 and hepatic failure (some with fatal outcome or requiring liver transplant) have been reported with NSAIDs, including celecoxib (see ADVERSE EFFECTS).

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

Physician and patients should remain alert for hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity. A patient with symptoms and/or signs suggesting liver dysfunction (e.g. nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms, 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 KUDEQ.

If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), KUDEQ 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 celecoxib. In controlled clinical trials the incidence of anaemia was 0.6% with celecoxib and 0.4% with placebo. Patients on long-term treatment with KUDEQ should have their haemoglobin or haematocrit checked if they exhibit any signs or symptoms of anaemia or blood loss. Celecoxib 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 NSAIDs has been reported in such aspirin-sensitive patients, KUDEQ 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 celecoxib (see ADVERSE EFFECTS). Therefore, KUDEQ 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.

**Effects on 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).

Based on the mechanism of action, the use of NSAIDs, including celecoxib, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAIDs, including celecoxib, should be considered.

**Use in Pregnancy**

Pregnancy Category: B3

There is no information on the use of celecoxib in pregnant women. KUDEQ 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 KUDEQ during the third trimester of pregnancy should be avoided, and KUDEQ 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 fetus. The effects of KUDEQ 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).

Inhibition of prostaglandin synthesis might adversely affect pregnancy. Epidemiological studies suggest an increased risk of spontaneous abortion after use of prostaglandin synthesis inhibitors in early pregnancy. In animals, administration of prostaglandin synthesis inhibitors has been shown to result in increased pre- and post-implantation loss.

**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.

**Paediatric Use**

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

**Use in the Elderly**

Of the total number of patients who received celecoxib 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.

### Genotoxicity

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.

### Carcinogenicity

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).

### Effects on Ability to Drive and Use Machines

The effect of celecoxib 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.

### Effects on 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 celecoxib 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).

Concomitant administration of celecoxib with inhibitors of CYP2C9 can lead to increases in plasma concentrations of celecoxib. Therefore, a dose reduction of celecoxib may be necessary when celecoxib is co-administered with CYP2C9 inhibitors.

Concomitant administration of celecoxib with inducers of CYP2C9 (such as rifampicin, carbamazepine and barbiturates) can lead to decreases in plasma concentrations of celecoxib. Therefore, a dose increase of celecoxib may be necessary when celecoxib is co-administered with CYP2C9 inducers.

Clinical pharmacokinetics study and *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.

**Antihypertensives including Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin II Antagonists, Diuretics and Beta-blockers**

Inhibition of prostaglandins may diminish the effect of antihypertensives including ACE inhibitors, angiotensin II antagonists (also known as angiotensin receptor blockers or ARBs), diuretics and beta-blockers. This interaction should be given consideration in patients taking KUDEQ concomitantly with these drugs.

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, angiotensin II antagonists or diuretics, may result in deterioration of renal function, including possible acute renal failure. Therefore, the concomitant administration of these drugs should be done with caution. Patients should be adequately hydrated and the clinical need to monitor the renal function should be assessed at the beginning of the concomitant treatment and periodically thereafter.

**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**

KUDEQ can be used with low dose aspirin. However, concomitant administration of aspirin with celecoxib may result in an increased rate of GI ulceration or other complications, compared to use of celecoxib 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 celecoxib were not different from those of the two comparators. Because of its lack of platelet effects, KUDEQ is not a substitute for aspirin for cardiovascular prophylaxis.

**Cyclosporin**

Because of their effect on renal prostaglandins, NSAIDs may increase the risk of nephrotoxicity with cyclosporin.

**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 PHARMACOLOGY, Pharmacokinetics, *Metabolism*). KUDEQ should be introduced at the lowest recommended dose in patients receiving fluconazole.

**Dextromethorphan and Metoprolol**

Concomitant administration of celecoxib resulted in increases in plasma concentrations of dextromethorphan and metoprolol (CYP2D6 substrates). These increases are due to celecoxib inhibition to the CYP2D6 substrate metabolism via CYP2D6. Therefore, the dose of drugs which are CYP2D6 substrate may need to be reduced when treatment with celecoxib is

initiated or increased when treatment with celecoxib is terminated (see PRECAUTIONS, Use with Drugs Metabolised by CYP2D6).

**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 celecoxib 200 mg BD as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when KUDEQ 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 celecoxib with an aluminium- and magnesium-containing antacid resulted in a reduction in plasma celecoxib concentrations with a decrease of 37% in $C_{max}$ and 10% in AUC.

**Methotrexate**

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

**Ketoconazole**

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

**Phenytoin**

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

**Oral Anticoagulants**

The concomitant use of NSAIDs with oral anticoagulants increases the risk of bleeding and should be given with caution. Oral anticoagulants include warfarin/coumarin-type and novel oral anticoagulants (e.g. apixaban, dabigatran, and rivaroxaban). Because increases in prothrombin time (INR) have been reported, anticoagulation/INR should be monitored, particularly in the first few days, after initiating or changing KUDEQ therapy in patients taking a warfarin/coumarin-type anticoagulant, 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 INR. However, in post-marketing experience, bleeding events have been reported, *some of them fatal*, predominantly in the elderly, in association with increases in INR in patients receiving

KUDEQ concurrently with warfarin or similar agents (see PRECAUTIONS, Gastrointestinal Effects).

### Other Drug Interactions

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

## ADVERSE EFFECTS

Of the celecoxib 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 celecoxib 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 celecoxib 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 Celecoxib Arthritis Trials

Table 5 lists all adverse events, regardless of causality, occurring in ≥ 2% of patients receiving celecoxib 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 Celecoxib Patients from Original Celecoxib Arthritis Trials**

| | Celecoxib (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% |
| Oedema peripheral | 2.1% | 1.1% | 2.1% | 1.0% | 3.5% |
| Injury | 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 celecoxib and 6.1% for patients receiving placebo. Among the most common reasons for discontinuation due to adverse events in the celecoxib treatment groups were dyspepsia and abdominal pain (cited as reasons for discontinuation in 0.8% and 0.7% of celecoxib 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 celecoxib (100 mg - 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:** | Hypersensitivity, asthenia, chest pain, cyst, oedema generalised, face oedema, fatigue, fever, hot flushes, influenza-like illness, 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, non-protein nitrogen increased, |

| | |
|---|---|
| | creatinine increased, alkaline phosphatase increased, weight increased |
| **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, cough, 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:** | Vision blurred, 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 celecoxib. Cases reported only in post-marketing experience are indicated in italics.

| | |
|---|---|
| **Cardiovascular:** | Syncope, cardiac failure congestive, ventricular fibrillation, cerebrovascular accident, peripheral gangrene, thrombophlebitis, *vasculitis, cerebral haemorrhage* |
| **Gastrointestinal:** | Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, oesophageal perforation, pancreatitis, ileus, oesophageal ulcer, gastric ulcer, duodenal ulcer |
| **Liver and biliary systems:** | Cholelithiasis, *hepatitis, hepatitis fulminant, jaundice, hepatic failure, hepatic necrosis, cholestasis, hepatitis* |

| | |
|---|---|
| | *cholestatic, liver transplant, hepatic enzymes increased* |
| **Haemic and lymphatic:** | Thrombocytopenia, *agranulocytosis, aplastic anaemia, pancytopenia, leukopenia* |
| **Metabolic:** | *Hypoglycaemia* |
| **Psychiatric:** | *Hallucination* |
| **Nervous system:** | Meningitis aseptic, ataxia, suicide, aggravated epilepsy, confusional state, *ageusia, anosmia* |
| **Renal:** | Renal failure acute, *tubulointerstitial nephritis, nephrotic syndrome, glomerulonephritis minimal lesion, hyponatraemia* |
| **Reproductive system:** | *Menstrual disorders,* infertility *female (female fertility decreased)* |
| **Respiratory:** | Pulmonary embolism, *pneumonitis* |
| **Skin:** | *Erythema multiforme, dermatitis exfoliative, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP)* |
| **Ear:** | Decreased hearing |
| **Eye:** | *Conjunctivitis* |
| **General:** | Sepsis, sudden death, *anaphylactic reaction, angioedema, dermatitis bullous.* |

**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 Drug Reactions from Polyp Prevention Trials**

The following additional adverse drug reactions in Table 6 were identified with 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*). Frequencies of ADRs in Table 6 were determined based on long-term polyp prevention studies and are defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%).

The ADRs in Table 6 are listed by system organ class are ranked by frequency in descending order.

**Table 6: Adverse Reactions Occurring in Celecoxib Patients from Long-term Studies involving Patients with Sporadic Adenomatous Polyps**

| **System Organ Class**<br>Frequency | **Adverse Drug Events** |
|---|---|
| **Infections and infestations**<br>Common<br>Uncommon | <br>Ear infection, fungal infection (primarily non-systemic)<br>Helicobacter infection, herpes zoster, erysipelas, wound infection, gingivitis, labyrinthitis, bacterial infection |
| **Neoplasms benign, malignant, and unspecified**<br>Uncommon | <br>Lipoma |
| **Psychiatric disorders**<br>Uncommon | <br>Sleep disorder |
| **Nervous system disorders**<br>Uncommon | <br>Cerebral infarction |
| **Eye disorders**<br>Uncommon | <br>Vitreous floaters, conjunctival haemorrhage |
| **Ear and labyrinth disorders**<br>Uncommon | <br>Hypoacusis |
| **Cardiac disorders**<br>Common<br>Uncommon | <br>Angina pectoris, myocardial infarction<br>Angina unstable, aortic valve incompetence, atherosclerosis coronary artery, sinus bradycardia, ventricular hypertrophy |
| **Vascular disorders**<br>Very Common<br>Uncommon | <br>Hypertension*<br>Deep vein thrombosis, haematoma |
| **Respiratory, thoracic, and mediastinal disorders**<br>Common<br>Uncommon | <br>Dyspnoea<br>Dysphonia |
| **Gastrointestinal disorders**<br>Very Common<br>Common<br><br><br>Uncommon | <br>Diarrhoea*<br>Nausea, gastro-oesophageal reflux disease, diverticulum, vomiting*, dysphagia, irritable bowel syndrome<br>Haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, stomatitis |
| **Hepatobiliary disorders**<br>Common | <br>Hepatic enzyme increased (includes alanine aminotransferase increased and aspartate aminotransferase increased)* |

| System Organ Class<br>Frequency | Adverse Drug Events |
|---|---|
| **Skin and subcutaneous tissue disorders**<br>Uncommon | Dermatitis allergic |
| **Musculoskeletal and connective tissue disorders**<br>Common<br>Uncommon | Muscle spasms<br>Synovial cyst |
| **Renal and urinary disorders**<br>Common<br>Uncommon | Nephrolithiasis<br>Nocturia |
| **Reproductive system and breast disorders**<br>Common<br>Uncommon | Vaginal haemorrhage, benign prostatic hyperplasia, prostatitis<br>Breast tenderness, dysmenorrhoea, ovarian cyst, menopausal symptoms |
| **General disorders and administration site conditions**<br>Uncommon | Oedema |
| **Investigations**<br>Common<br>Uncommon | Blood creatinine increased, prostatic specific antigen increased, weight increased<br>Blood potassium increased, blood sodium increased, blood testosterone decreased, haematocrit decreased, haemoglobin increased |
| **Injury, poisoning and procedural complications**<br>Uncommon | Foot fracture, lower limb fracture, epicondylitis, tendon rupture, fracture |

* Hypertension, vomiting, diarrhoea and hepatic enzyme increased are included in Table 6 because these events 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 with regards to efficacy, risk factors and ongoing need for treatment.

**Adults**

The following 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 400 mg then 200 mg once or twice daily as required for up to 5 days.

The effective dose in this patient population is 200 mg 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, KUDEQ should be introduced at half the recommended dose.

There is no clinical experience in patients with severe hepatic impairment. Therefore, the use of KUDEQ 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 PHARMACOLOGY, Pharmacokinetics).

### Children and Adolescents

KUDEQ 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 PHARMACOLOGY, Pharmacokinetics).

## OVERDOSAGE

Clinical experience of overdose is limited. No overdoses of celecoxib 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.

### Signs and Symptoms

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.

### Treatment of Overdosage

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 on 131126 for advice on the management of an overdose.

## PRESENTATION AND STORAGE CONDITIONS

**KUDEQ** capsules are presented in PVC/Al or PVC/Aclar/Al blister packs. The blistered product is placed in a cardboard outer carton.

**KUDEQ (celecoxib) 100 mg capsules:** Opaque, white capsules with 2 blue bands marked 7767 and 100. Available in cartons of 10s, 20s, 50s and 60s.

**KUDEQ (celecoxib) 200 mg capsules:** Opaque, white capsules with 2 gold bands marked 7767 and 200. Available in cartons of 10s, 20s, 30s, 50s, 60s and 120s.

Not all strengths or pack sizes may be distributed in Australia.

**Storage Conditions**

Store below 25°C.

## NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114.

## POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4).

## DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

19 March 2014

## DATE OF MOST RECENT AMENDMENT

17 September 2015

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