

## ONSENAL

### Celecoxib 200mg and 400mg Capsules

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#### Presentation

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

400 mg Capsules: Opaque, white capsules with 2 green bands marked 7767 and 400.

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#### Uses

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#### Actions

##### **Pharmacotherapeutic group: M01AH Coxibs.**

Celecoxib is a member of a class of agents which has a mechanism of action that inhibits prostaglandin synthesis primarily by inhibition of cyclooxygenase 2 (COX-2). At therapeutic concentrations in humans celecoxib does not inhibit cyclooxygenase 1 enzyme (COX-1). COX-2 is induced in response to inflammatory stimuli. This leads to the synthesis and accumulation of inflammatory prostanoids, in particular prostaglandin E<sub>2</sub>, causing inflammation, oedema and pain. In animal models, celecoxib acts as an anti-inflammatory, analgesic and anti-pyretic 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. 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.

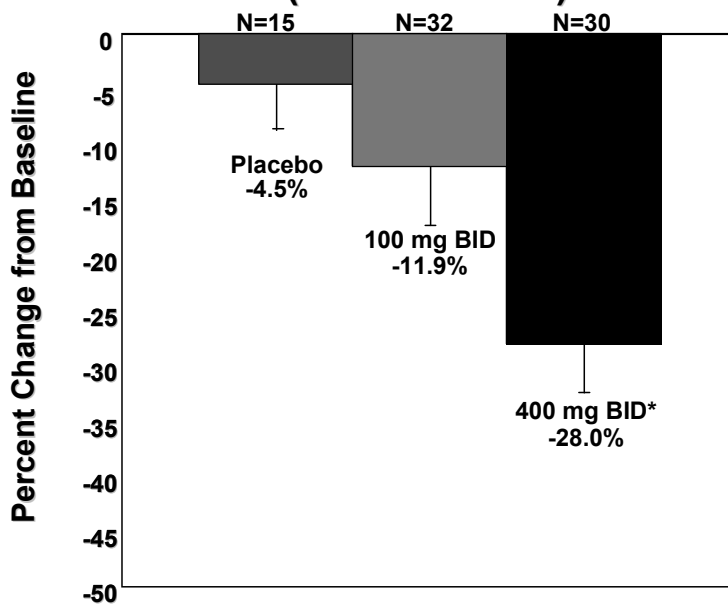
#### Clinical trials

##### **Familial Adenomatous Polyposis (FAP):**

Celecoxib was evaluated to reduce the number of adenomatous colorectal polyps. A randomised, double-blind placebo-controlled study was conducted in 83 patients with FAP. The study population included 58 patients with a prior subtotal or total colectomy and 25 patients with an intact colon. Thirteen patients had the attenuated FAP phenotype.

One area in the rectum and up to four areas in the colon were identified at baseline for specific follow-up, and polyps were counted at baseline and following six months of treatment. The mean reduction in the number of colorectal polyps was 28% for celecoxib 400 mg BD, 12% for celecoxib 100 mg BD and 5% for placebo. The reduction in polyps observed with celecoxib 400 mg BD was statistically superior to placebo at the six-monthly time point (p=0.003). (See Figure 1.)

**Figure 1**  
**Percent Change from Baseline in**  
**Number of Colorectal Polyps**  
**(FAP Patients)**



\* p=0.003 versus placebo

The adverse event profile reported for the patients in this FAP trial was similar to that reported for patients in the arthritis controlled trials.

### Special Studies:

#### Celecoxib Long term Arthritis Safety Study (CLASS)

##### Study Design

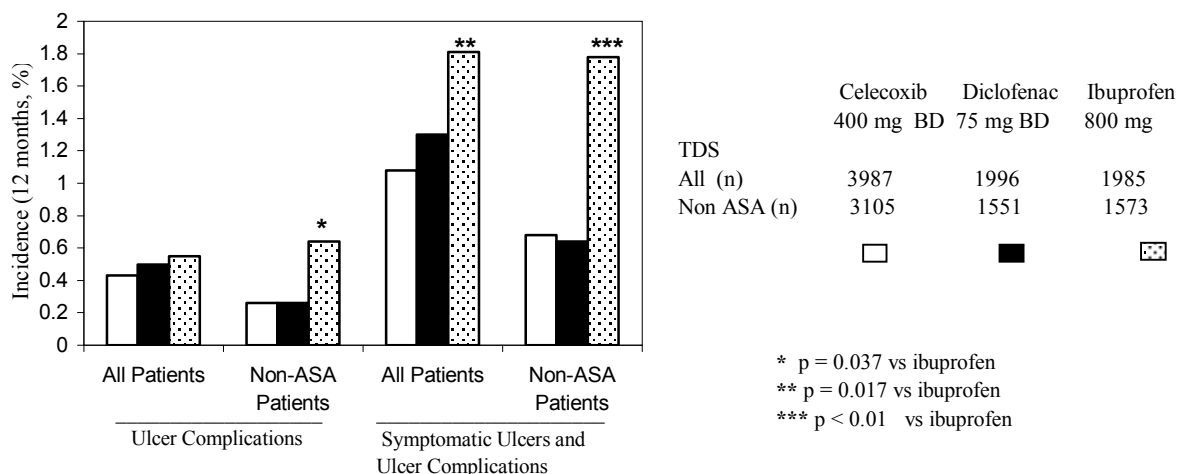
A prospective long-term outcome study was conducted in approximately 5800 OA patients and 2200 RA patients. The primary endpoint of this outcome study was the incidence of *complicated ulcers* (gastrointestinal bleeding, perforation or obstruction) in celecoxib treated patients compared to each comparator. 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 (Figure 2). 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.

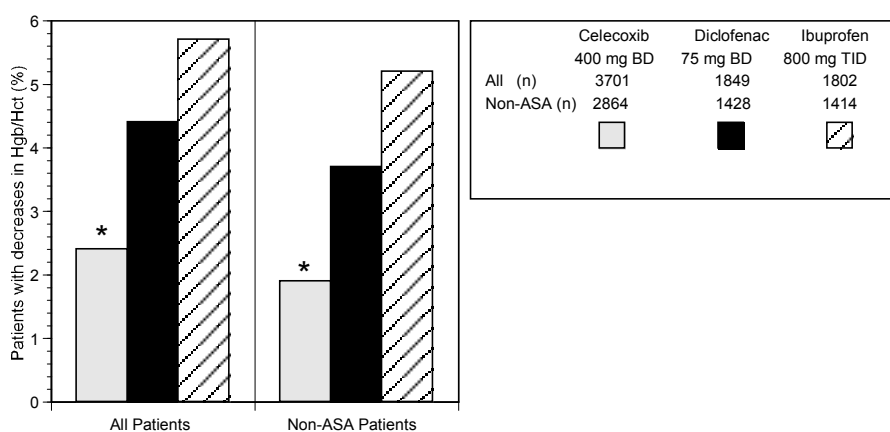
**Figure 2: Incidence of symptomatic ulcers and ulcer complications** Celecoxib was also



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 3).

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 3: Incidence of clinically relevant decreases in haemoglobin and/or haematocrit**



\*p<0.05 celecoxib vs ibuprofen and diclofenac

Further experience on the safety of celecoxib has been gained in clinical trials in Rheumatoid Arthritis (RA), Osteoarthritis (OA) and Dysmenorrhoea – refer to **Interactions** and **Adverse Effects**.

## Upper Gastrointestinal Complications

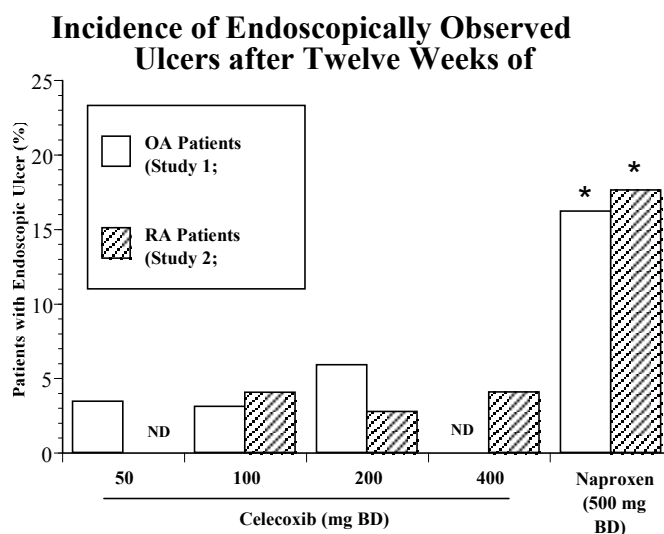
In the original registration studies, the incidence of serious upper gastrointestinal complications (bleeding, perforation, gastric outlet obstruction) with celecoxib is not significantly different from placebo and is approximately 8-fold less than with non-specific COX inhibitors.

## 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 4 and Table 1 summarise the incidence of endoscopic ulcers in two 12-week studies that enrolled patients in whom baseline endoscopies revealed no ulcers.

**Figure 4:**



ND = Not

\* Significantly different from all other treatments;

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%

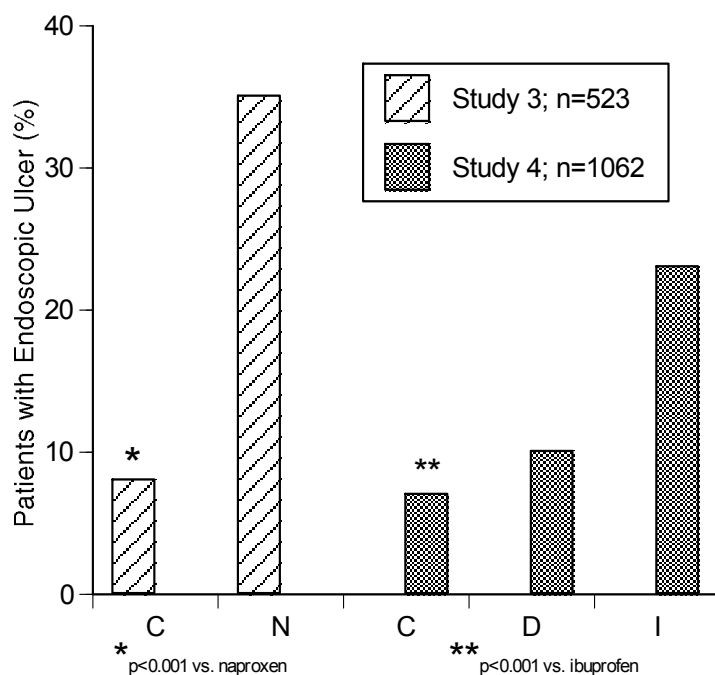
**Table 1: Incidence of Gastroduodenal Ulcers from Endoscopic Studies in OA and RA Patients**

	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 5 and Table 2 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 5: Cumulative Incidence of Gastroduodenal Ulcers Based on 4 Serial Endoscopies Over 12 Weeks**



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

**Table 2: Incidence of Gastroduodenal Ulcers from 3-Month Serial Endoscopy Studies in OA and RA Patients**

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

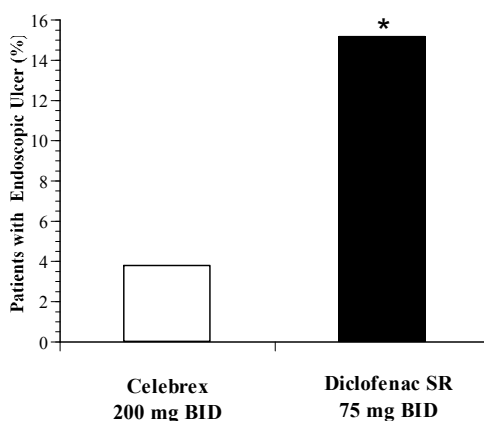
\* p ≤ 0.05 Celecoxib vs. naproxen based on interval and cumulative analyses

† 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 6.

**Figure 6:**

**Prevalence of Endoscopically Observed Gastroduodenal Ulcers after Six Months of Treatment in Patients with Rheumatoid Arthritis**



\* 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.

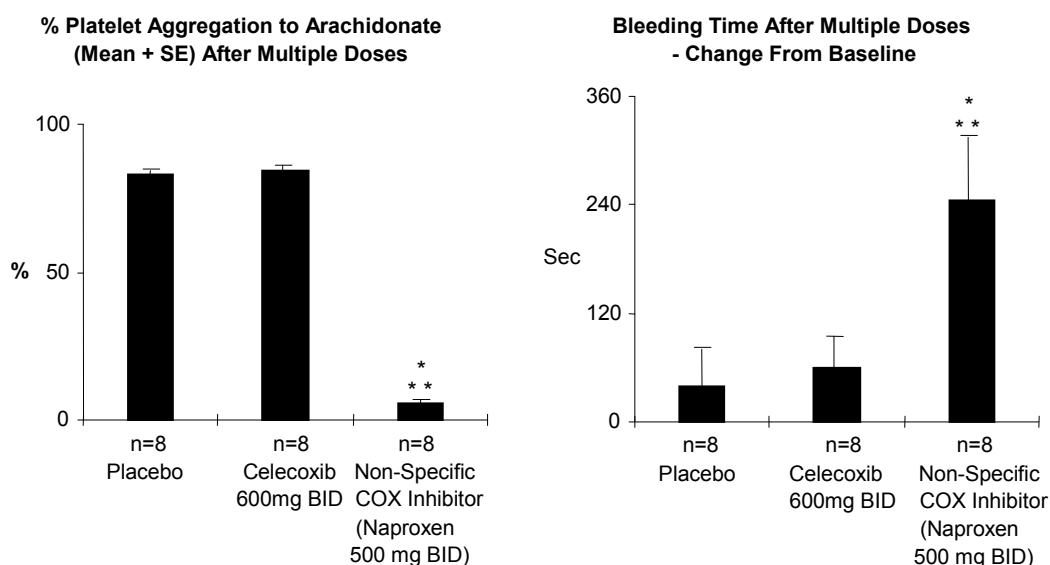
Serious clinically significant upper GI bleeding has been observed in patients receiving celecoxib in controlled and open-labelled trials, albeit infrequently. Among 5,285 patients who received celecoxib in the original arthritis controlled clinical trials of 1 to 6 months duration (most were 3

month studies) at a daily dose of 200 mg or more, 2 patients (0.04%) experienced significant UGI bleeding. Patients most at risk of developing an ulcer complication were the elderly ( $\geq 75$  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 5 endoscopic studies were taking aspirin ( $\leq 325$  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.

**Platelet Function:** At total daily doses of 1200 mg (higher than recommended therapeutic doses) for up to 7 days duration, celecoxib had no effect on platelet aggregation and bleeding time compared to placebo. Active controls (non-specific COX inhibitors ie naproxen, diclofenac, ibuprofen) all significantly reduced platelet aggregation and prolonged bleeding time.

**Figure 7**



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

**Gastrointestinal Safety Meta-Analysis from Osteoarthritis and Rheumatoid Arthritis Studies:**

An analysis of 31 randomised controlled clinical studies in osteoarthritis and rheumatoid arthritis, involving 39,605 patients with osteoarthritis (N = 25,903), rheumatoid arthritis (N = 3,232) or patients with either condition (N = 10,470) compared the incidence of GI adverse events in celecoxib treated patients with placebo or NSAIDs (including naproxen, diclofenac and ibuprofen). The incidence of clinical ulcers and ulcer bleeds with celecoxib 200 - 400 mg total daily dose was 0.2% compared with an incidence of 0.6% with NSAIDs (RR = 0.35; 95% CI 0.22 - 0.56).

## **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 (Prevention of Sporadic Colorectal Adenomas with Celecoxib) and the PreSAP trial (Prevention of Colorectal Sporadic 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 relative risks 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).<sup>67</sup> The increases for both celecoxib dose groups versus placebo were mainly driven by myocardial infarction.

In the PreSAP trial, the relative risk 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).

### **Cardiovascular Safety - Ongoing Clinical Trials:**

Preliminary data from the Alzheimer's prevention study (ADAPT) did not show a significantly increased cardiovascular risk with celecoxib 400 mg once daily and 200 mg twice daily respectively, compared to placebo. This information will be updated as final data become available.

### **Cardiovascular Safety - Meta-analysis from Chronic Usage Studies:**

No long-term controlled clinical study specifically designed to assess the CV safety of chronic celecoxib dosing of any duration has been conducted. However, a meta-analysis of safety data (adjudicated, investigator-reported serious adverse events) from 39 completed celecoxib clinical studies of up to 65 weeks in duration has been conducted, representing 41,077 patients [23,030 (56.1%) patients exposed to celecoxib 200-800 mg total daily dose (TDD), 13,990 (34.1%) patients exposed to non-selective NSAIDs, and 4057 (9.9%) patients exposed to placebo]

In this analysis, the adjudicated event rate for the composite endpoint of CV death, non-fatal myocardial infarction and non-fatal stroke was similar between celecoxib (N=19,773; 0.96 events/100 patient-years) and non-selective NSAID (N=13,990; 1.12 events/100 patient-years) treatment (RR=0.90, 95% CI 0.60 - 1.33). This pattern of effect was maintained with or without aspirin use ( $\leq 325$  mg). The adjudicated event rate of non-fatal myocardial infarction trended higher (RR=1.76, 95% CI 0.93 - 3.35); however that of stroke trended lower (RR= 0.51, 95% CI 0.23 - 1.10), and that of cardiovascular death was comparable (RR=0.57, 95% CI 0.28 - 1.14) for celecoxib compared to combined non-selective NSAIDs.

In this analysis, the adjudicated event rate for the composite endpoint of CV death, non-fatal myocardial infarction and non-fatal stroke was 1.42/100 patient-years for celecoxib (N=7,462) and 1.20/100 patient-years for placebo (N=4,057) treatment (RR=1.11, 95% CI 0.47 - 2.67). This pattern of effect was maintained with or without aspirin use ( $\leq 325$  mg). The incidence of non-fatal myocardial infarction trended higher (RR=1.56, 95% CI 0.21 - 11.90), as did that of cardiovascular death (RR=1.26, 95% CI 0.33 - 4.77), and that of stroke was similar (RR=0.80, 95% CI 0.19 - 3.31) for celecoxib compared to placebo.

## Cardiovascular Safety – CLASS Trial

Cardiovascular safety outcomes were evaluated in the CLASS trial (see above 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-ASA users at nine months in each of the three treatment groups were less than 1 %. The cumulative rates for myocardial infarction in non-ASA 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 the risk to a similar degree.

## Pharmacokinetics

**Absorption** When celecoxib is given under fasting conditions, peak plasma concentrations are reached after approximately 2-3 hours. 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 **Food Effects**). Absolute bioavailability studies have not been conducted because of celecoxib's low solubility in aqueous media. The relative oral solubility of celecoxib capsules compared with a suspension is about 99%. With multiple dosing, steady state conditions are reached on or before day 5.

**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. 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. At doses up to 200 mg BD celecoxib can be administered without regard to the timing of meals. In FAP patients, the recommended higher dose (400 mg BD) should be administered with food to improve absorption.

**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 metabolism is primarily mediated via cytochrome P450 2C9. Three metabolites have been identified in human plasma, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate.

Cytochrome P450 2C9 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as those homozygous for the CYP2C9\*3 polymorphism.

In a pharmacokinetic study of celecoxib 200 mg administered once daily in healthy volunteers, genotyped as either CYP2C9\*1/\*1, CYP2C9\*1/\*3, or CYP2C9\*3/\*3, the median  $C_{max}$  and AUC 0-24 of celecoxib on day 7 were approximately 4-fold and 7-fold, respectively, in subjects genotyped as CYP2C9\*3/\*3 compared to other genotypes. In three separate single dose studies, involving a total of 5 subjects genotyped as CYP2C9\*3/\*3, single-dose AUC 0-24 increased by

approximately 3-fold compared to normal metabolizers. It is estimated that the frequency of the homozygous \*3/\*3 genotype is 0.3 – 1.0% among different ethnic groups.

Patients who are known or suspected to be poor P450 2C9 metabolisers based on previous history should be administered ONSENAL with caution. Consider starting treatment at half the lowest recommended dose. (See **Dosage and Administration and Drug Interactions**)

**Elimination:** Celecoxib is eliminated predominantly by hepatic metabolism with little (<3%) unchanged drug recovered in the urine and faeces. 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 is 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.

**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. The daily recommended dose of ONSENAL capsules should be reduced by approximately 50% in FAP patients with moderate hepatic impairment. Patients with severe hepatic impairment have not been studied. The use of ONSENAL in patients with severe hepatic impairment is not recommended.

**Renal Impairment:** In elderly volunteers with age related reductions in glomerular filtration rate (GFR) (mean GFR > 65 ml/min/1.73m<sup>2</sup>) and in patients with chronic stable renal insufficiency (GFR 35-60 ml/min/1.73m<sup>2</sup>) 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 C<sub>max</sub> and a 50% higher AUC than those of younger subjects. In elderly females, the C<sub>max</sub> 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:** Celecoxib capsules have not been investigated in paediatric patients below 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.

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## Indications

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To reduce the number of adenomatous colorectal polyps in FAP, as an adjunct to usual care (e.g. endoscopic surveillance, surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the

effects of ONSENAL treatment will persist after ONSENAL is discontinued. The efficacy and safety of celecoxib treatment in patients with FAP beyond six months has not been studied.

The decision to prescribe a selective COX-2 inhibitor should only be made after assessment of the individual patient's overall risks.

The cardiovascular risks of the selective COX-2 inhibitors may increase with dose and duration of exposure. 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.

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## Contraindications

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Known hypersensitivity to celecoxib or any of the excipients contained in the ONSENAL capsules. (see **Further Information**).

Demonstrated allergic-type reactions to sulphonamides.

ONSENAL should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking acetyl salicylic acid (ASA) 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 **Warnings and Precautions-Anaphylactoid Reactions**).

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

Use of celecoxib in the peri-operative period is contraindicated in patients undergoing cardiac or major vascular surgery.

Use of celecoxib is contraindicated in patients who have previously had a myocardial infarction or stroke.

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## Warnings and Precautions

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### Cardiovascular adverse effects

Use of COX-2 inhibitors (of which celecoxib is one) has been associated with increased risk of cardiovascular adverse events (myocardial infarction and stroke) (see **Clinical Trials**).

Two large, controlled clinical trials of a different COX-2 selective inhibitor for the treatment of pain in the first 10 - 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. In the absence of comparable data with celecoxib, it may be assumed that patients at high risk of cardiovascular disease (including patients with diabetes, ischaemic heart disease, cardiac failure, hyperlipidaemia, hypertension, or smokers) who are undergoing any major surgery may face an increased risk of developing a cardiovascular event. Patients with significant

risk factors for cardiovascular events should only be treated with celecoxib after careful consideration of the patient's overall risk and the potential risks and benefits of therapy.

Prescribers should inform the individual patient of the possible increased risks when prescribing celecoxib for patients at high risk of cardiovascular adverse events. 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. Celecoxib is not a substitute for cardiovascular prophylaxis because of its lack of effect on platelets; therefore, concurrent anti-platelet therapies should not be discontinued. There is no evidence that concurrent use of aspirin decreases the risk of cardiovascular adverse events associated with COX-2 inhibitors, including celecoxib.

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

Celecoxib exhibited a low incidence of gastroduodenal ulceration and serious clinically significant GI events within clinical trials (see **Clinical trials- Special Studies**).

Serious GI toxicity, such as peptic ulceration, perforation and bleeding, sometimes severe and occasionally fatal, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal 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 nonsteroidal 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.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Upper gastrointestinal perforations, ulcers or bleeds have occurred in patients treated with celecoxib.

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 ONSENAL should be used.

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. It is unclear how this finding applies to celecoxib. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

There is further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications), when celecoxib is taken concomitantly with aspirin (even at low doses).

In patients on concurrent therapy with warfarin or similar agents, serious bleeding events have been reported. Because increases in prothrombin time (INR) have been reported, anti-coagulant activity should be monitored after initiating treatment with celecoxib or changing the dose. If INR increases, it may be sufficient to reduce the dose of warfarin in order to manage the interaction.

There is no definitive evidence that the concomitant administration of histamine H<sub>2</sub>-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of ONSENAL 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. ONSENAL 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 Warnings 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 the cases within the first month of treatment. ONSENAL 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:** NSAIDs, including celecoxib may cause renal toxicity. Clinical trials with celecoxib have shown renal effects similar to those observed with comparator NSAIDs. 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 nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Such patients should be carefully monitored while receiving treatment with celecoxib. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

Clinical trials with celecoxib 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<sub>2</sub> and 6-keto-PGF<sub>1 $\alpha$</sub>  (a prostacyclin metabolite) but leaves serum thromboxane B<sub>2</sub> (TXB<sub>2</sub>) and urinary excretion of 11-dehydro-TXB<sub>2</sub>, a thromboxane metabolite (both COX-1 products) unaffected. Caution should be used when initiating treatment with ONSENAL in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with ONSENAL. No information is available regarding the use of celecoxib in patients with advanced kidney disease. Therefore, treatment with ONSENAL is not recommended in these patients. If ONSENAL 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 institution 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 and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including celecoxib (see **Adverse Effects** – post-marketing experience). 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. 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 celecoxib. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), ONSENAL should be discontinued.

**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 celecoxib 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 -Special Studies-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 nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, ONSENAL 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**). As with all NSAIDs, celecoxib may exacerbate pre-existing hypertension, cardiac failure or oedema, and the treatment of these conditions may be compromised. Therefore, ONSENAL should be used with caution in patients with fluid retention, hypertension, or heart failure and other conditions predisposing to, or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

**Familial Adenomatous Polyposis (FAP):** Treatment with celecoxib in FAP has not been shown to reduce the risk of gastrointestinal cancer or the need for prophylactic colectomy or other FAP-related surgeries. Therefore, the usual care of FAP patients should not be altered because of the

concurrent administration of ONSENAL. In particular, the frequency of routine endoscopic surveillance should not be decreased and prophylactic colectomy or other FAP-related surgeries should not be delayed.

It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of ONSENAL treatment will persist after ONSENAL is discontinued. The efficacy and safety of celecoxib treatment in patients with FAP beyond six months have not been studied (see **Uses – Actions**).

**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.

### **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<sub>0-24 h</sub> at 400 mg BD), 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 as measured by the AUC<sub>0-24 h</sub> 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<sub>0-24 h</sub> at 400 mg BD).

### **Pregnancy and Lactation**

#### **Pregnancy Category: B3**

There is no information on the use of celecoxib in pregnant women. ONSENAL 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 foetal lambs and to contribute to maintenance of patency. Therefore, use of ONSENAL during the third trimester of pregnancy should be avoided. The effects of celecoxib 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<sub>0-24 h</sub> at 400 mg BD). 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<sub>0-24 h</sub> was similar to that in humans dosed at 400 mg BD. At the threshold dose of 60 mg/kg/day in rabbits, AUC<sub>0-24 h</sub> was slightly below that in humans dosed at 400 mg BD. Celecoxib had a marginal effect on parturition, 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<sub>0-24 h</sub> 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 in nursing infants from celecoxib, 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 ONSENAL 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.

## Other

### Use in the Elderly

Of the total number of patients who received celecoxib in all 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 Celecoxib Long Term Arthritis Safety Study has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In clinical studies comparing renal function as measured by the GFR, BUN 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

Safety and effectiveness in paediatric patients below the age of 18 years have not been evaluated.

### Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

During the controlled clinical trials, there was an increased incidence of hyperchloremia in patients receiving celecoxib compared with patients on placebo. Other laboratory abnormalities that occurred more frequently in the patients receiving celecoxib included hypophosphatemia, and elevated BUN. These laboratory abnormalities were also seen in patients who received comparator NSAIDs in these studies. The clinical significance of these abnormalities has not been established.

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## Interactions

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### **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 half the lowest recommended 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** 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 celecoxib concomitantly with ACE-inhibitors and/or angiotensin II antagonists. **Furosemide:** Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

**Aspirin:** Celecoxib 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 – Special Studies – Upper Gastrointestinal Complications**). Because of its lack of platelet effects, celecoxib 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**). ONSENAL 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 celecoxib 200 mg BD as compared to subjects receiving lithium alone. Patients on lithium treatment should be closely monitored when ONSENAL 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.

**Warfarin:** In patients on concurrent therapy with warfarin or similar agents, serious bleeding events, some of them fatal, predominantly in elderly, have been reported. Because increases in prothrombin time (INR) have been reported, anti-coagulant activity should be monitored after initiating treatment with celecoxib or changing the dose. If INR increases, it may be sufficient to reduce the dose of Warfarin in order to manage the interaction (see **Warning and Precautions – Gastrointestinal Effects**).

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## **Adverse Effects**

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Most of the information on adverse reactions has been collected from clinical trials in arthritis. The doses used in the arthritis trials were usually half that recommended for FAP.

Of the celecoxib treated patients in controlled trials, approximately 4,250 were patients with OA, approximately 2,100 were patients with RA, and approximately 1,050 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 the controlled trial in familial adenomatous polyposis**

The adverse event profile reported for the 83 patients with familial adenomatous polyposis enrolled in the randomised, controlled clinical trial was similar to that reported for patients in the arthritis controlled trials (refer to **Adverse events from original celecoxib arthritis trials**). Intestinal anastomotic ulceration was the only new adverse event reported in the FAP trial, regardless of causality, and was observed in 3 of 58 patients (one at 100 mg BD, and two at 400 mg BD) who had prior intestinal surgery. **Adverse events from original celecoxib arthritis trials**

Adverse events from controlled trials: Table 3 lists all adverse events, regardless of causality, occurring in  $\geq 2\%$  of patients receiving celecoxib from 12 controlled studies conducted in patients with OA or RA that included a placebo and/or a positive control group.

**Table 3: Adverse Events Occurring in  $\geq 2\%$  Of celecoxib Patients From Original celecoxib arthritis trials**

	<b>Celecoxib</b> (100-200 mg BD or 200 mg once daily) (N=4146)	<b>Placebo</b> (N=1864)	<b>Naproxen</b> 500 mg BD (N=1366)	<b>Diclofenac</b> 75 mg BD (N=387)	<b>Ibuprofen</b> 800 mg TDS (N=345)
<b>Gastrointestinal</b>					
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%
<b>Body as a whole</b>					
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%
<b>Central and peripheral nervous system</b>					
Dizziness	2.0%	1.7%	2.6%	1.3%	2.3%
Headache	15.8%	20.2%	14.5%	15.5%	15.4%
<b>Psychiatric</b>					
Insomnia	2.3%	2.3%	2.9%	1.3%	1.4%
<b>Respiratory</b>					
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%
<b>Skin</b>					
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 a Celecoxib Long term Arthritis Safety Study was similar to those reported in the arthritis controlled trials.

**The following adverse events occurred in 0.1 - 1.9% of patients regardless of causality.**

**Celecoxib (100 - 200 mg BD or 200 mg once daily)**

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

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

**Other serious adverse reactions which occur rarely (<0.1%), regardless of causality:**

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

<b>Cardiovascular:</b>	Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, <i>vasculitis</i> , ischaemic stroke*.
<b>Gastrointestinal:</b>	Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, oesophageal perforation, pancreatitis, ileus
<b>Liver and Biliary system:</b>	Cholelithiasis, <i>hepatitis, jaundice, liver failure</i> , elevation of hepatic enzymes.
<b>Haemic and lymphatic:</b>	Thrombocytopenia, <i>agranulocytosis, aplastic anaemia, pancytopenia, leukopenia</i>
<b>Metabolic:</b>	Hypoglycaemia
<b>Psychiatric:</b>	<i>Hallucinations</i>
<b>Nervous system:</b>	<i>Ageusia, anosmia, aseptic meningitis</i> , ataxia, suicide, aggravated epilepsy
<b>Renal:</b>	<i>Acute renal failure, interstitial nephritis</i>
<b>Reproductive system and breast disorders:</b>	<i>Menstrual disorders</i>
<b>Skin:</b>	<i>Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis</i>
<b>Ear:</b>	Decreased hearing
<b>General:</b>	Sepsis, sudden death, <i>anaphylactoid reaction</i> , angioedema, bullous eruption

\*In a pooled analysis of 20 placebo-controlled studies with duration greater than 2 weeks up to 1 year in patients with OA and RA, the excess rate of myocardial infarction in patients treated with celecoxib 200 or 400 mg daily over placebo was 0.7 events per 1000 patients (Rare) and there was no excess of strokes.

In preliminary data from two studies in patients with colorectal polyps treated with celecoxib 400 mg daily (see **Clinical Trials – Cardiovascular Safety**) the excess rate over placebo of myocardial infarction over 3 years was 7 events per 1000 patients (Uncommon). In the same studies, the excess rate for clearly identified ischaemic stroke for the 400 mg daily dose (not including events that were haemorrhagic or of unknown aetiology) was 0.5 event per 1000 over 3 years (Rare). For all strokes, there was no increased event rate with celecoxib compared with placebo.

### **Adverse events from analgesia and dysmenorrhea studies**

Approximately 1,700 patients were treated with celecoxib in analgesia and dysmenorrhea studies. All patients in post-oral surgery pain and dysmenorrhea studies received a single dose of study medication. Doses up to 600 mg/day were studied in primary dysmenorrhea and post-orthopedic surgery pain studies. The types of adverse events in the analgesia and dysmenorrhea studies were similar to those reported in arthritis studies. In approximately 700 patients treated with celecoxib in the post-general and orthopedic surgery pain studies, the most commonly reported adverse events were nausea, vomiting, headache, dizziness and fever.

**Adverse events from polyp prevention trials:** The following additional adverse reactions in Table 4 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 reactions 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 4 Adverse Events Occurring in ONSENAL Patients From Long-Term Studies Involving Patients With Sporadic Adenomatous Polyps**

<b>System Organ Class Frequency</b>	<b>Adverse Drug Reaction</b>
<b>Infections and infestations</b> Common  Uncommon	Ear infection, fungal infection (primarily non-systemic)  Helicobacter infection, herpes zoster, erysipelas, wound infection, gingival infection, labyrinthitis, bacterial infection
<b>Neoplasms benign, malignant, and unspecified</b> Uncommon	Lipoma
<b>Psychiatric disorders</b> Uncommon	Sleep disorder
<b>Nervous system disorders</b> Uncommon	Cerebral infarction
<b>Eye disorders</b> Uncommon	Vitreous floaters, conjunctival haemorrhage
<b>Ear and labyrinth disorders</b> Uncommon	Hypoacusis
<b>Cardiac disorders</b> Common	Angina pectoris, myocardial infarction

Uncommon	Angina unstable, aortic valve incompetence, coronary artery atherosclerosis, sinus bradycardia, ventricular hypertrophy
<b>Vascular disorders</b> Very Common Uncommon	Hypertension Deep vein thrombosis, haematoma
<b>Respiratory, thoracic, and mediastinal disorders</b> Common Uncommon	Dyspnoea Dysphonia
<b>Gastrointestinal disorders</b> Very Common Common Uncommon	Diarrhoea Nausea, gastro-oesophageal reflux disease, diverticulum, vomiting*, dysphagia, irritable bowel syndrome Haemorrhoidal haemorrhage, frequent bowel movements, mouth ulceration, stomatitis
<b>Skin and subcutaneous tissue disorders</b> Uncommon	Dermatitis allergic
<b>Musculoskeletal and connective tissue disorders</b> Common Uncommon	Muscle spasms Ganglion
<b>Renal and urinary disorders</b> Common Uncommon	Nephrolithiasis Nocturia
<b>Reproductive system and breast disorders</b> Common Uncommon	Benign prostatic hyperplasia, prostatitis Vaginal haemorrhage, breast tenderness, dysmenorrhoea, ovarian cyst, menopausal symptoms
<b>General disorders and administration site conditions</b> Uncommon	Oedema
<b>Investigations</b> Common Uncommon	Blood creatinine increased, prostatic specific antigen increased, weight increased Blood potassium increased, blood sodium increased, blood testosterone decreased, haematocrit decreased, haemoglobin increased
<b>Injury, poisoning and procedural complications</b> Uncommon	Foot fracture, lower limb fracture, epicondylitis, tendon rupture, fracture

\*Hypertension, vomiting and diarrhoea are included in Table 4 because they were reported more frequently in these studies, which were of 3-year duration, compared to Table 3, which includes adverse reactions from studies of 12-week duration.

**Other adverse events:** 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.

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## Dosage and Administration

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### Adults

To reduce the number of adenomatous colorectal polyps in patients with FAP, the recommended oral dose is 400 mg twice per day. This 400 mg BD dose should be taken with food to improve absorption (see **Pharmacokinetics**). Usual medical care for FAP patients should be continued while on ONSENAL.

**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.

The daily recommended dose of ONSENAL capsules in FAP patients with moderate hepatic impairment (Child-Pugh Class II) should be reduced by approximately 50%.

There is no clinical experience in patients with severe hepatic impairment and the use of ONSENAL is not recommended in these patients (See **Pharmacokinetics, Contraindications and Warnings and Precautions**).

**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 and Warnings and Precautions**).

**Children:** Celecoxib has not been studied in subjects under 18 years old.

**CYP2C9 Poor Metabolizers:** Patients who are known, or suspected to be CYP2C9 poor metabolizers based on previous history/experience with other CYP2C9 substrates should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose. (See Sections **Interaction and Pharmacokinetic properties, Metabolism**.)

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## Overdosage

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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, and 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 NSAID 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 may reduce absorption of the drug if given within one or two 1-hour of ingestion. 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, alkalization 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

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## **Pharmaceutical Precautions**

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### **Incompatibilities**

Incompatibilities with other medicines - None known.

### **Shelf life**

ONSENAL 200 mg and 400 mg capsules have a shelf-life of 36 months when stored in PVC/Aclar/Aluminium foil blisters or PVC/Aluminium foil blisters, in an outer carton below 25°C.

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## **Medicine Classification**

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Prescription Only Medicine.

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## **Package Quantities**

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ONSENAL is available as:

200 mg capsules in cartons of 60's.

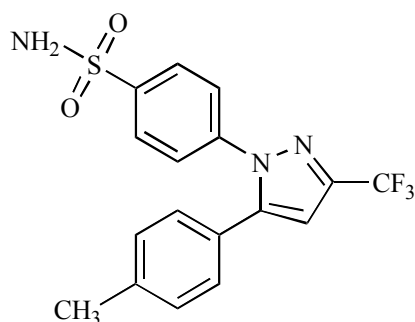
400 mg capsules in cartons of 60's.

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## Further Information

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The chemical structure of celecoxib is as shown below:



$C_{17}H_{14}F_3N_3O_2S$  M.W. = 381.38  
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide

ONSENAL 200 mg and 400 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 and 400 mg capsule); Brilliant Blue FCF CI 42090 Aluminium Lake (400 mg capsule).

Celecoxib is weakly acidic with a pK<sub>a</sub> in water of 11.1 and is practically insoluble in water. Celecoxib does not contain a chiral centre.

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## Name and Address

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Pfizer New Zealand Ltd  
PO Box 3998  
Auckland, NEW ZEALAND

Toll Free number: 0800 736 363

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## Date of Preparation

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11 December 2007

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