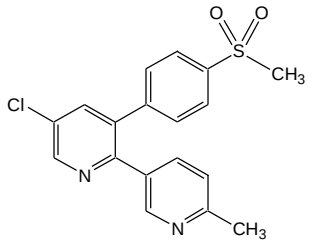
PRODUCT INFORMATION

ARCOXIA® Tablets
(etoricoxib, MSD)

NAME OF THE MEDICINE

ARCOXIA tablets contain etoricoxib, which is described chemically as 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine. The empirical formula is $C_{18}H_{15}ClN_2O_2S$. The molecular weight is 358.84. The CAS Registry Number is 202409-33-4. The structural formula is:



DESCRIPTION

Etoricoxib is a white to off-white powder. Etoricoxib is freely soluble in methanol, tetrahydrofuran, dimethyl sulfoxide, methyl ethyl ketone, dimethyl formamide, and chloroform. Etoricoxib is soluble in isopropyl acetate, ethanol and toluene, sparingly soluble in 2-propanol, and practically insoluble in water.

Each tablet of ARCOXIA for oral administration contains either 30, 60, 90 or 120 mg of etoricoxib and the following excipients; calcium hydrogen phosphate (anhydrous), carnauba wax, croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, titanium dioxide, glycerol triacetate. The 30, 60 and 120 mg tablets also contain iron oxide yellow CI77492 and indigo carmine CI73015.

PHARMACOLOGY

Pharmacotherapeutic Group: M01AH Coxibs

Mechanism of Action

Etoricoxib is a member of a new class of agents called Coxibs. Etoricoxib is a potent, orally active cyclooxygenase-2 (COX-2) specific inhibitor within, and significantly above, the clinical dose range. Two isoforms of cyclooxygenase have been identified: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is responsible for prostaglandin-mediated normal physiologic functions such as gastric cytoprotection and platelet aggregation. Inhibition of COX-1 by nonselective NSAIDs has been associated with gastric damage and inhibition of platelet aggregation. COX-2 has been shown to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. Selective inhibition of COX-2 by etoricoxib (within the clinical dose range) decreases these clinical signs and symptoms with decreased potential for GI toxicity and effects on platelet aggregation.

Across clinical pharmacology studies, ARCOXIA produced dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150 mg daily.

The influence on gastroprotective COX-1 activity was also assessed in a clinical study where prostaglandin synthesis was measured in gastric biopsy samples from subjects administered either ARCOXIA 120 mg daily, naproxen 500 mg twice daily, or placebo. ARCOXIA did not inhibit gastric prostaglandin synthesis as compared to placebo. In contrast, naproxen inhibited gastric prostaglandin synthesis by approximately 80% compared with placebo. These data further support the COX-2 selectivity of ARCOXIA.

Platelet Function

Multiple doses of ARCOXIA up to 150 mg administered daily up to nine days had no effect on bleeding time relative to placebo. Similarly, bleeding time was not altered in a single dose study with ARCOXIA 250 or 500 mg. There was no inhibition of *ex vivo* arachidonic acid- or collagen-induced platelet aggregation at steady state with doses of ARCOXIA up to 150 mg. These findings are consistent with the COX-2 selectivity of etoricoxib.

The difference in antiplatelet activity between some COX-1 inhibiting NSAIDs and COX-2 selective inhibitors may be of clinical significance in patients at risk of thromboembolic events. COX-2 inhibitors reduce the formation of systemic (and therefore possibly endothelial) prostacyclin without affecting platelet thromboxane. The clinical relevance of these observations has not been established.

Pharmacokinetics

Absorption

Orally administered etoricoxib is well absorbed. The mean oral bioavailability is approximately 100%. Following 120 mg once-daily dosing to steady state, the peak plasma concentration (geometric mean C_{max}= 3.6mcg/mL) was observed at approximately 1hour (T_{max}) after administration to fasted adults. The geometric mean $AUC_{0\text{-}24hr}$ was 37.8 mcg•hr/mL. The pharmacokinetics of etoricoxib are linear across the clinical dose range.

A standard meal had no clinically meaningful effect on the extent or rate of absorption of a dose of etoricoxib 120 mg. In clinical trials, etoricoxib was administered without regard to food.

The pharmacokinetics of etoricoxib in 12 healthy subjects were similar (comparable AUC, C_{max} within approximately 20%) when administered alone, with a magnesium/aluminium hydroxide antacid, or a calcium carbonate antacid (approximately 50 mEq acid-neutralising capacity).

Distribution

Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 mcg/mL. The volume of distribution at steady state (V_{dss}) is approximately 120 L in humans.

Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

Etoricoxib is extensively metabolised with <1% of a dose recovered in urine as the parent drug. Five metabolites have been identified in humans. Metabolism *in vitro* involves conversion primarily to the 6'-hydroxymethyl derivative, mainly (*ca.* 60%) by CYP3A4, with less contribution by CYPs 1A2, 2C9, 2C19 and 2D6 (*ca.* 40% collectively). The 6'-hydroxymethyl derivative is

further metabolised by oxidation to the principal metabolite, the 6'-carboxylic acid derivative of etoricoxib. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1 (see also INTERACTIONS WITH OTHER MEDICINES).

Excretion

Following administration of a single 25 mg radiolabelled intravenous dose of etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in faeces, mostly as metabolites. Less than 2% was recovered as unchanged drug.

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of once-daily administration of 120 mg, with an accumulation ratio of approximately 2, corresponding to an accumulation half-life of approximately 22 hours. The plasma clearance is estimated to be approximately 50 mL/min.

Gender

The pharmacokinetics of etoricoxib are similar between men and women (see DOSAGE AND ADMINISTRATION).

Elderly

Pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young. No dosage adjustment is necessary for elderly patients (for elderly patients with hepatic impairment see DOSAGE AND ADMINISTRATION, *Hepatic Insufficiency*).

Race

There is no clinically important effect of race on the pharmacokinetics of etoricoxib (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency

Patients with mild hepatic insufficiency (Child-Pugh score 5-6) administered etoricoxib 60 mg once daily had an approximately 16% higher mean AUC as compared to healthy subjects given the same regimen. Patients with moderate hepatic insufficiency (Child-Pugh score 7-9) administered etoricoxib 60 mg *every other day* had similar mean AUC to the healthy subjects given etoricoxib 60 mg once daily, etoricoxib 30 mg once daily has not been studied in this population. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score > 9) (see DOSAGE AND ADMINISTRATION, *Hepatic Insufficiency*).

Renal Insufficiency

The pharmacokinetics of a single dose of etoricoxib 120 mg in patients with moderate-to-severe renal insufficiency and patients with end-stage renal disease on haemodialysis were not significantly different from those in healthy subjects. Haemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 mL/min).

Paediatric Patients

The pharmacokinetics of etoricoxib in paediatric patients (<12 years of age) have not been studied.

In a pharmacokinetic study (N=16) conducted in adolescents (aged 12 to 17) the pharmacokinetics in adolescents weighing 40 to 60 kg given etoricoxib 60 mg once daily and in adolescents > 60 kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily. Safety and effectiveness of etoricoxib in paediatric patients have not been established.

CLINICAL TRIALS

Osteoarthritis (OA)

ARCOXIA has demonstrated significant reduction in joint pain compared to placebo. ARCOXIA was evaluated for the treatment of the signs and symptoms of OA of the knee and hip in approximately 3,300 patients enrolled in six placebo-controlled Phase III clinical trials with ARCOXIA 30 mg (12 weeks and 26 weeks) or 60 mg (52 weeks). The pivotal Phase III studies included: two placebo-controlled studies of etoricoxib 30 mg and ibuprofen 2400 mg, two placebo-controlled studies of etoricoxib 30 mg and celecoxib 200 mg and two placebo-controlled studies of etoricoxib 60 mg and naproxen 1000 mg.

Treatment with ARCOXIA resulted in improvement in pain, function (mobility) and inflammation (stiffness and tenderness), as assessed by the WOMAC (Western Ontario and McMaster Universities) osteoarthritis questionnaire, and patient and investigator assessments. Once-daily treatment, when administered in the morning with ARCOXIA 30 mg or 60 mg, was associated with a significant reduction in joint stiffness upon first awakening the next morning.

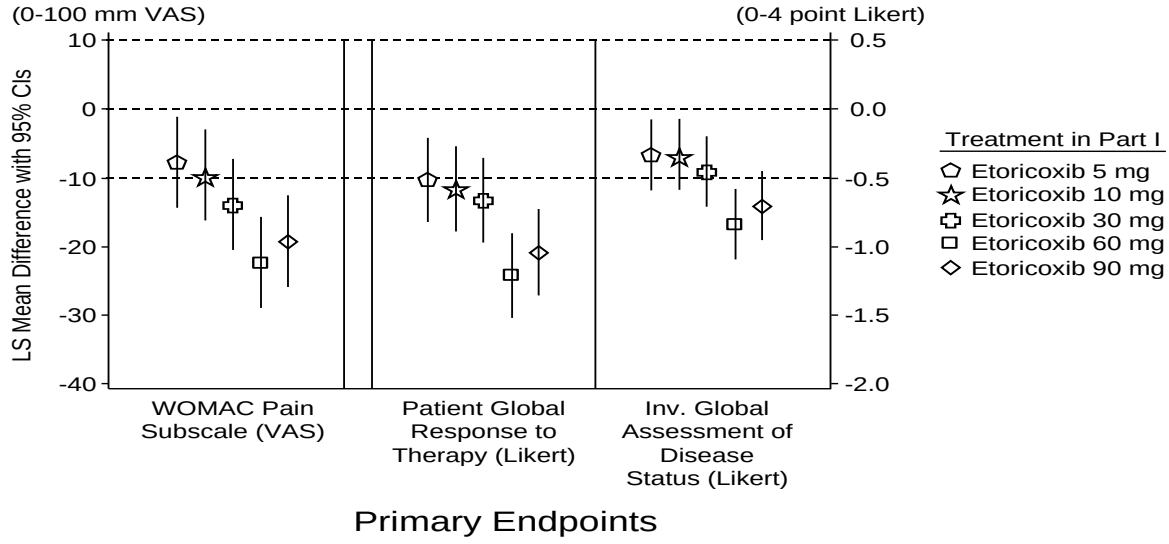
The effectiveness of ARCOXIA 30 mg was shown to be comparable to ibuprofen 800 mg three times daily as well as to celecoxib 200 mg daily (see Table 1).

Table 1: WOMAC Pain and Patient Global Assessment Responses Time-Weighted Average Response Over the 12-Week Treatment Period Phase III Etoricoxib 30 mg OA Studies (Protocols 071, 073, 076, and 077)

Treatment Group	Baseline Mean	LS Mean Change from Baseline (95% CI)
Protocol 071		
Pain Subscale (WOMAC) (0- to 100-mm VAS)		
Placebo (n=101)	69.50	-16.36 (-20.59, -12.13)
Etoricoxib 30 mg (n=212)	68.72	-26.90 (-29.97, -23.83)
Ibuprofen 2400 mg (n=209)	67.78	-25.25 (-28.40, -22.11)
Patient Global Assessment of Disease Status (0- to 100-mm VAS)		
Placebo (n=100)	72.60	-16.53 (-20.99, -12.06)
Etoricoxib 30 mg (n=211)	72.24	-27.89 (-31.13, -24.65)
Ibuprofen 2400 mg (n=209)	70.53	-26.53 (-29.83, -23.22)
Protocol 073		
Pain Subscale (WOMAC) (0- to 100-mm VAS)		
Placebo (n=109)	64.66	-16.47 (-20.55, -12.40)
Etoricoxib 30 mg (n=220)	66.46	-28.14 (-31.23, -25.04)
Ibuprofen 2400 mg (n=211)	64.74	-24.10 (-27.20, -20.99)
Patient Global Assessment of Disease Status (0- to 100-mm VAS)		
Placebo (n=107)	66.93	-17.85 (-22.41, -13.29)
Etoricoxib 30 mg (n=220)	70.14	-29.50 (-32.91, -26.10)
Ibuprofen 2400 mg (n=211)	69.88	-25.97 (-29.39, -22.54)
Protocol 076		
Pain Subscale (WOMAC) (0- to 100-mm VAS)		
Placebo (n=126)	66.63	-12.31 (-16.31, -8.32)
Etoricoxib 30 mg (n=228)	67.36	-27.38 (-30.46, -24.30)
Celecoxib 200 mg (n=236)	67.48	-24.26 (-27.29, -21.23)
Patient Global Assessment of Disease Status (0- to 100-mm VAS)		
Placebo (n=126)	69.10	-13.99 (-18.16, -9.83)
Etoricoxib 30 mg (n=228)	72.18	-30.44 (-33.66, -27.21)
Celecoxib 200 mg (n=236)	71.25	-26.39 (-29.55, -23.23)
Protocol 077		
Pain Subscale (WOMAC) (0- to 100-mm VAS)		
Placebo (n=112)	66.44	-15.21 (-19.49, -10.94)
Etoricoxib 30 mg (n=243)	68.68	-26.77 (-29.68, -23.86)
Celecoxib 200 mg (n=246)	67.27	-26.91 (-29.86, -23.96)
Patient Global Assessment of Disease Status (0- to 100-mm VAS)		
Placebo (n=111)	72.30	-12.48 (-16.88, -8.09)
Etoricoxib 30 mg (n=243)	72.98	-28.34 (-31.33, -25.35)
Celecoxib 200 mg (n=246)	70.11	-28.40 (-31.42, -25.37)
LS Mean=Least-squares mean, CI=Confidence interval, VAS=Visual analog scale, WOMAC=Western Ontario McMaster Universities.		

The dose-ranging study, Protocol 007, included 617 OA patients randomised to placebo or etoricoxib doses of 5, 10, 30, 60, and 90 mg. Protocol 007 demonstrated that all etoricoxib doses (5, 10, 30, 60, 90 mg) were significantly better than placebo for the 3 primary endpoints: the WOMAC Pain Subscale, the Investigator Global Assessment of Disease Status, and the Patient Global Assessment of Response to Therapy, as shown in the accompanying figure (see Figure 1). The 60 mg dose met three out of three predefined efficacy criteria, whereas the 30 mg dose met two out of three predefined efficacy criteria; and etoricoxib 60 mg demonstrated significantly greater efficacy than etoricoxib 30 mg. Etoricoxib 90 mg did not demonstrate greater efficacy than the etoricoxib 60 mg dose.

Figure 1: OA Dose-Ranging Study (Protocol 007)
Analysis of Primary Endpoints (6 week treatment period)



The effectiveness of ARCOXIA 60 mg was shown to be comparable to naproxen 500 mg twice daily for treatment of the signs and symptoms of OA (see Table 2). Onset of efficacy was evaluated only in the 60 mg studies and was demonstrated within the first 24 hours of initiating treatment. In patients with OA of the hand, reductions in pain and stiffness, and improvement in physical function, as measured by the AUSCAN questionnaire were superior to placebo and similar to that in patients treated with naproxen.

Table 2: WOMAC Pain and Patient Global Assessment Responses Time-Weighted Average Response Over the 12-Week Treatment Period Phase III Etoricoxib 60 mg OA Studies (Protocols 018, 019)

Treatment Group	Baseline Mean	LS Mean Change From Baseline (95% CI)
Protocol 018		
Pain Subscale (WOMAC) (0- to 100-mm VAS)		
Placebo (n=55)	71.14	-15.74 (-21.54, -9.94)
Etoricoxib 60 mg (n=220)	68.87	-30.41 (-33.51, -27.31)
Naproxen 1000 mg (n=217)	69.01	-32.27 (-35.42, -29.11)
Patient Global Assessment of Disease Status (0- to 100-mm VAS)		
Placebo (n=55)	71.75	-10.50 (-16.51, -4.50)
Etoricoxib 60 mg (n=220)	67.61	-27.10 (-30.31, -23.90)
Naproxen 1000 mg (n=217)	68.69	-29.10 (-32.36, -25.83)
Protocol 019		
Pain Subscale (WOMAC) (0- to 100-mm VAS)		
Placebo (n=56)	68.70	-15.33 (-20.70, -9.96)
Etoricoxib 60 mg (n=223)	64.92	-25.76 (-28.58, -22.94)
Naproxen 1000 mg (n=219)	65.66	-25.32 (-28.13, -22.50)
Patient Global Assessment of Disease Status (0- to 100-mm VAS)		
Placebo (n=56)	73.55	-16.59 (-22.26, -10.92)
Etoricoxib 60 mg (n=222)	66.86	-25.93 (-28.90, -22.95)
Naproxen 1000 mg (n=218)	67.83	-24.18 (-27.15, -21.21)
LS Mean=Least-squares mean, CI=Confidence interval, VAS=Visual analog scale, WOMAC=Western Ontario McMaster Universities.		

The clinical benefit of both ARCOXIA 30 mg and 60 mg was maintained for the duration of the studies.

Acute Gouty Arthritis

ARCOXIA 120 mg once daily, over an eight-day treatment period, demonstrated reductions in joint pain and inflammation (tenderness, swelling, and erythema) comparable to indomethacin 50 mg three times daily in the treatment of patients experiencing moderate to extreme pain (approximately 150 patients) during an attack of acute gouty arthritis. Reduction in pain was observed as early as four hours after initiation of treatment (the first determination).

Acute Pain including Post-Operative Dental Pain and Primary Dysmenorrhoea

In single-dose clinical studies which treated approximately 1,200 patients, ARCOXIA relieved moderate-to-severe pain in acute analgesic models of post-operative dental pain and primary dysmenorrhoea. The analgesic effect of a 120 mg dose of ARCOXIA was similar to a maximum analgesic dose of naproxen sodium (550 mg) or ibuprofen (400 mg) and greater than paracetamol (600 mg) with codeine (60 mg). The onset of analgesia with ARCOXIA occurred as early as 24 minutes after dosing and persisted for as long as 24 hours.

In a multiple-dose post-dental surgery study (Protocol 092), ARCOXIA 90 mg administered once daily for up to three days provided a significantly greater analgesic effect compared to placebo. ARCOXIA 90 mg provided a shorter time to onset and longer duration of pain relief, greater peak pain relief, in addition to a lower use of rescue analgesic medication following the initial first day dose compared to placebo. ARCOXIA 90 mg was non-inferior to ibuprofen 600 mg four times daily, and superior to paracetamol/codeine 600 mg/60 mg four times daily in total pain relief.

Special Studies

Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Study Program

The MEDAL Program was a prospectively designed Cardiovascular (CV) Safety Outcomes program of pooled data from three individual, randomised, double-blind active comparator (diclofenac)-controlled trials (MEDAL study, EDGE II and EDGE). The MEDAL Program also evaluated upper and lower GI safety. The Program consisted of 34,701 OA and RA patients treated with etoricoxib 60 mg daily (OA) or etoricoxib 90 mg daily (OA and RA, 1.5 to 3 times the doses recommended for OA) versus diclofenac 150 mg daily for a mean period of approximately 18 months; approximately 12,800 had more than 24 months of exposure with some patients receiving up to 42 months of treatment.

Patients enrolled in the MEDAL Program had a wide range of baseline cardiovascular and gastrointestinal risk factors. Approximately 47% of patients had a history of hypertension, approximately 12% had a history of symptomatic atherosclerotic cardiovascular disease (ASCVD) and approximately 38% of patients had an increased cardiovascular risk at baseline (defined as having either a previous history of symptomatic ASCVD or ≥ 2 Cardiovascular Risk Factors from among the following 5 [history of hypertension, history of diabetes mellitus, history of dyslipidaemia, family history of cardiovascular disease, cigarette use]). Patients with a recent history of myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention within 6 months preceding enrolment were excluded. Use of gastroprotective agents and low-dose aspirin were permitted in the studies with approximately 50% of the patients on gastroprotective agents and approximately 35% of the patients on low-dose aspirin. In the studies, efficacy of etoricoxib 60 mg and 90 mg was shown to be comparable to diclofenac.

The cardiovascular and gastrointestinal safety data are summarised below (Table 3). Other important safety data, including renovascular data, is described in Adverse Reactions.

Cardiovascular data: The MEDAL Program showed that the rates of confirmed thrombotic cardiovascular serious adverse events (consisting of cardiac, cerebrovascular, and peripheral vascular events) were comparable between etoricoxib and diclofenac (see Table 3). For the primary endpoint of confirmed thrombotic CV events, the relative risk between etoricoxib and diclofenac was 0.95 (95% CI: 0.81, 1.11) in the pre-specified primary analysis. The event rates for individual types of thrombotic events (e.g. myocardial infarction and stroke) were also similar between etoricoxib and diclofenac. The rates were similar between etoricoxib and diclofenac over the entire duration of the study, including in the subset of patients who were on treatment for greater than 24 months. There were no discernible differences in thrombotic event rates between etoricoxib and diclofenac across all subgroups analysed, including patient categories across a range of baseline cardiovascular risk. CV mortality, as well as overall mortality, was similar between the etoricoxib and diclofenac treatment groups.

Table 3: Overall Rates of Confirmed Thrombotic CV Events (Pooled MEDAL Program)

	Etoricoxib (N=16,819) 25,836 Patient-Years	Diclofenac (N=16,483) 24,766 Patient-Years	Between Treatment Comparison
	Rate† (95% CI)	Rate† (95% CI)	Relative Risk (95% CI)
Total number of patients with Endpoint	1.24 (1.11, 1.38)	1.30 (1.17, 1.45)	0.95 (0.81, 1.11)
Cardiac Events	0.71 (0.61, 0.82)	0.78 (0.68, 0.90)	0.90 (0.74, 1.10)
zCerebrovascular Events	0.34 (0.28, 0.42)	0.32 (0.25, 0.40)	1.08 (0.80, 1.46)
Peripheral Vascular Events	0.20 (0.15, 0.27)	0.22 (0.17, 0.29)	0.92 (0.63, 1.35)
†Events per 100 Patient-Years. N=total number of patients; CI=confidence interval			

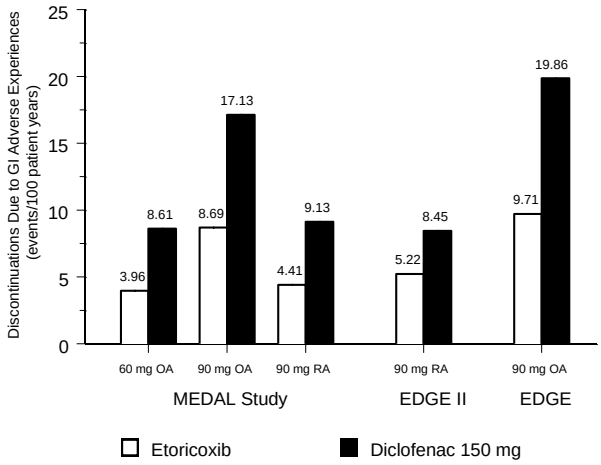
Gastrointestinal data: Overall upper GI events were defined as perforations, ulcers and bleeds. The subset of overall upper GI events considered complicated included perforations, obstructions, and complicated bleeding; the subset of upper GI events considered uncomplicated included uncomplicated bleeds and uncomplicated ulcers. The rates per hundred patient–years of confirmed upper GI clinical events (perforations, ulcers, and bleeds; PUBs) were 0.67 (95% CI 0.57, 0.77) with etoricoxib and 0.97 (95% CI 0.85, 1.10) with diclofenac, yielding a relative risk of 0.69 (95% CI 0.57, 0.83). No significant difference was observed in rates of complicated upper GI clinical events between etoricoxib and diclofenac (0.30 vs 0.32 per hundred patient-years). As the risk for upper GI events increases with age, the rate for these events in elderly patients was evaluated. The largest risk reduction was observed in patients ≥ 75 years of age; the rate per hundred patient-years for a confirmed upper GI event was lower for etoricoxib compared to diclofenac (1.35 [95% CI 0.94, 1.87] vs 2.78 [95% CI 2.14, 3.56]). The rates for confirmed upper GI events in patients taking concomitant low-dose aspirin and/or gastroprotective agents were also evaluated and are presented in Table 4. The rates of confirmed lower GI clinical events were 0.32 (95% CI 0.25, 0.39) vs 0.38 (95% CI 0.31, 0.46) per hundred patient-years for etoricoxib vs diclofenac, yielding a relative risk of 0.84 (95% CI 0.63, 1.13).

Table 4: Confirmed Upper GI Events (Pooled MEDAL Program)

	Etoricoxib	Diclofenac
	Rate† (95% CI)	Rate† (95% CI)
Overall Rate [Relative Risk 0.69 (0.57,0.83)]	0.67 (0.57, 0.77)	0.97 (0.85, 1.10)
Concomitant Low Dose Aspirin Use		
No	0.38 (0.29, 0.48)	0.73 (0.60, 0.87)
Yes	1.14 (0.94, 1.37)	1.37 (1.15, 1.63)
Concomitant Gastroprotective Agents Use‡		
No	0.63 (0.49, 0.79)	0.83 (0.67, 1.02)
Yes	0.70 (0.57, 0.84)	1.07 (0.91, 1.25)
†Rate = Events per 100 patient-years = (n/PYR)x100. CI=Confidence Interval. ‡Proton pump inhibitors and misoprostol accounted for approximately 96% of patients taking gastroprotective agents		

GI tolerability, defined as patients discontinuing the study for any clinical (e.g., dyspepsia, abdominal pain, ulcer) or laboratory (e.g., increased ALT, AST) GI adverse experience including hepatic events, was also evaluated in each individual study within the MEDAL Program. The EDGE and EDGE II studies assessed GI tolerability as the primary endpoint. They compared etoricoxib 90 mg daily and diclofenac 150 mg daily in patients with OA (EDGE) and RA (EDGE II). The MEDAL Study compared GI tolerability between etoricoxib 60 mg (OA) or 90 mg (OA and RA) to diclofenac 150 mg daily as a secondary objective. In all three studies, etoricoxib demonstrated superior GI tolerability compared to diclofenac (p-values < 0.001; see Figure 2). The GI tolerability benefit for etoricoxib was significant both for the clinical and for the laboratory components that make up this composite endpoint.

Figure 2: GI Tolerability



Hepatic-related adverse events resulting in discontinuation were evaluated in each individual study within the MEDAL Program. The incidences of discontinuations were significantly lower in the etoricoxib 60 and 90 mg treatment groups compared with the diclofenac 150 mg treatment groups for both OA and RA patients in all three studies.

Additional Thrombotic Cardiovascular Safety Data

In a combined analysis of all Phase IIB to Phase V clinical studies of 4 weeks duration or longer (excluding the MEDAL Program Studies), there was no discernible difference in the rate of confirmed serious thrombotic cardiovascular events between patients receiving etoricoxib ≥30 mg or non-naproxen NSAIDs. However, the rate of these events was higher in patients receiving etoricoxib compared with those receiving naproxen 500 mg twice daily, with a statistically significant increase in relative risk with etoricoxib with respect to the Anti-Platelet Trialists' Collaboration (APTC) combined endpoint. In the studies which directly compared etoricoxib to placebo (6 to 12 weeks duration), there was no discernable difference in the event rates between patients receiving etoricoxib or placebo; however there were few events and the studies were limited in duration (see PRECAUTIONS, *Cardiovascular effects*).

Table 5 Etoricoxib Development Program
Summary of Confirmed Thrombotic Events and Confirmed APTC Combined Endpoint

Comparisons	N	n/PYR†	Rate‡ (95% CI)	Relative Risk (95% CI)
Confirmed Thrombotic Events				
Etoricoxib	3,940	9/810	1.11 (0.51, 2.11)	1.07 (0.36, 3.22)
Placebo	2,337	5/450	1.11 (0.36, 2.59)	--
Etoricoxib	2,147	14/1,815	0.77 (0.42, 1.29)	0.73 (0.27, 1.98)
Non-Naproxen NSAIDs	1,470	6/649	0.92 (0.34, 2.01)	--
Etoricoxib	1,960	34/2,480	1.37 (0.95, 1.92)	1.70 (0.91, 3.18)
Naproxen 1000 mg	1,497	14/1,727	0.81 (0.44, 1.36)	--
Confirmed APTC Combined Endpoint				
Etoricoxib	3,940	7/810	0.86 (0.35, 1.78)	1.95 (0.37, 19.19)
Placebo	2,337	2/450	0.44 (0.05, 1.60)	--
Etoricoxib	2,147	11/1,817	0.61 (0.30, 1.08)	0.80 (0.25, 2.59)
Non-Naproxen NSAIDs	1,470	4/649	0.62 (0.17, 1.58)	--
Etoricoxib	1,960	27/2,481	1.09 (0.72, 1.58)	2.72 (1.18, 6.27)
Naproxen 1000 mg	1,497	7/17,28	0.41 (0.16, 0.83)	--

† Patient-years at risk.
‡ Per 100 PYR.
APTC = Antiplatelet Trialists' Collaboration ; CI = Confidence interval; PYR = Patient-years at risk.
APTC combined endpoint includes (cardiovascular, haemorrhagic and unknown death, non-fatal myocardial ischaemia, and non-fatal stroke).

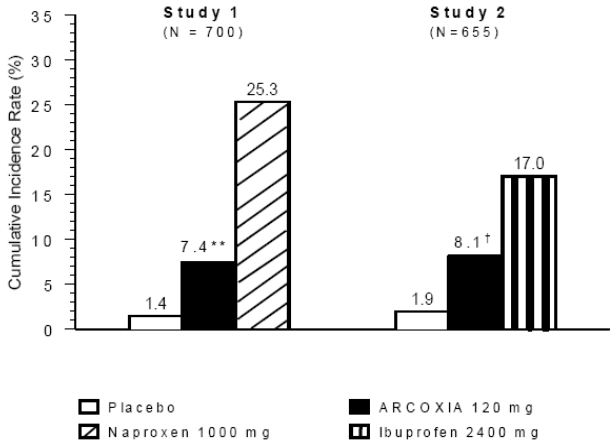
Additional Gastrointestinal Safety Data

The following special studies were conducted to evaluate whether ARCOXIA, a COX-2 selective inhibitor, is associated with less GI toxicity than nonselective NSAIDs.

Upper Endoscopy in Patients with Rheumatoid Arthritis or Osteoarthritis

The cumulative incidence of gastroduodenal ulcers was significantly lower in patients treated with ARCOXIA 120 mg once daily than in patients treated with either of two nonselective NSAIDs (naproxen 500 mg twice daily or ibuprofen 800 mg three times daily) in two 12-week double-blind endoscopy studies. Seven hundred patients with either OA or RA were treated in Study 1, while 655 patients with OA were treated in Study 2. Patients treated with ARCOXIA had a higher cumulative incidence of ulcers as compared to patients treated with placebo (see Figure 3 for the results of these studies).

Figure 3
Life-Table Cumulative Incidence of Gastroduodenal Ulcer ≥3 mm* Over 12 Weeks for Both Endoscopy Studies
(Intent-to-Treat)



* Results of analyses using a ≥5 mm gastroduodenal ulcer endpoint were consistent.
** p<0.001 versus naproxen 500 mg twice daily
† p=0.007 versus ibuprofen 800 mg three times daily.

Both endoscopy studies included the following patients at a higher risk for GI ulcers: patients with active *Helicobacter pylori* infection; baseline gastroduodenal erosions; prior history of perforation, ulcer or bleed (PUB); and/or concomitant use of corticosteroids. Four hundred patients (28%) were 65 years of age and older. The advantage of ARCOXIA versus naproxen or ibuprofen was maintained in these higher risk subgroups.

Gastrointestinal Safety Combined Analysis

In a combined analysis of all Phase IIb to V clinical studies of 4 weeks duration or longer (excluding the MEDAL Program Studies), the rate of PUB events (gastroduodenal perforations, symptomatic gastrointestinal ulcers or upper GI bleeds) for combined doses of etoricoxib ranging from 30 mg to 120 mg daily (N = 4,107 patients with a mean duration of treatment of approximately 220 days) was compared to non-selective NSAIDs (naproxen 1000 mg daily, diclofenac 150 mg daily and ibuprofen 2400 mg daily; total N = 2,967 patients with a mean duration of treatment of approximately 182 days). The event rates of confirmed PUBs for the etoricoxib group were approximately half of those in the nonselective NSAIDs group during the first year of treatment (1.13 events per hundred-patient years for etoricoxib compared to 2.64 events per hundred patient-years for NSAIDs; relative risk 0.47 [95%CI: 0.28, 0.76]). The results were consistent over the entire follow-up period. In the combined analysis, the magnitude of the risk reduction for the complicated events (primarily a result of upper GI haemorrhages) was generally consistent over the entire treatment period with results for overall upper GI clinical events (relative risk 0.57 [95%CI: 0.31, 1.07]), although the number of events is more limited.

Gastrointestinal Clinical Tolerability Combined Analysis

A pre-specified, combined analysis of eight clinical trials of approximately 4,000 patients with OA, RA or chronic low back pain assessed the incidence rate for the following endpoints: 1) discontinuation for upper GI symptoms; 2) discontinuation for any GI adverse events; 3) new use of gastroprotective medications (including H_2 receptor antagonists, misoprostol, and proton pump inhibitors); and 4) new use of any GI medications. There was an approximate 50% risk reduction for these endpoints in patients treated with ARCOXIA (60, 90 or 120 mg daily) as compared to patients treated with nonselective NSAIDs (naproxen 500 mg twice daily or diclofenac 50 mg three times daily). There were no statistically significant differences between ARCOXIA and placebo.

Assessment of Faecal Occult Blood Loss in Healthy Subjects

To assess mucosal integrity throughout the gastrointestinal tract, faecal blood loss with ARCOXIA 120 mg daily, ibuprofen 2400 mg daily, and placebo was compared in a study utilising ^{51}Cr-tagged red blood cells in 62 healthy males. After four weeks of treatment with ARCOXIA 120 mg, there was no significant increase in the amount of faecal blood loss compared with placebo-treated subjects. In contrast, ibuprofen 2400 mg daily produced a significant increase in faecal blood loss as compared to subjects treated with placebo and subjects treated with ARCOXIA.

Renal Function Study in Elderly Subjects

A randomised, double-blind, placebo-controlled, parallel-group study evaluated the effects of 15 days of treatment of etoricoxib (90 mg), celecoxib (200 mg twice daily), naproxen (500 mg twice daily) and placebo on urinary sodium excretion, blood pressure, and other renal function parameters in subjects 60 to 85 years of age on a 200-mEq/day sodium diet. Etoricoxib, celecoxib, and naproxen had similar effects on urinary sodium excretion over the 2 weeks of treatment. All active comparators showed an increase relative to placebo with respect to systolic blood pressures; however, etoricoxib was associated with a statistically significant increase at Day 14 when compared to celecoxib and naproxen (mean change from baseline for systolic blood pressure: etoricoxib 7.7 mmHg, celecoxib 2.4 mmHg, naproxen 3.6 mmHg).

INDICATIONS

ARCOXIA is indicated for:

- Symptomatic treatment of the signs and symptoms of osteoarthritis (OA)
- Treatment of acute gouty arthritis
- Treatment of acute pain, including that related to primary dysmenorrhoea and minor dental procedures

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks.

CONTRAINDICATIONS

ARCOXIA is contraindicated in patients with:

- hypersensitivity to any component of this product. A history of asthma, urticaria, or other allergic reactions after taking aspirin or other NSAIDs.
- congestive heart failure (NYHA II-IV).

- hypertension whose blood pressure is persistently elevated above 140/90mmHg and has not been adequately controlled.
- established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease (including patients who have recently undergone coronary artery bypass graft surgery or angioplasty).
- severe hepatic dysfunction (serum albumin < 25 g/l or Child-Pugh score ≥ 10, see *footnote*)
- active peptic ulceration or gastrointestinal (GI) bleeding
- estimated creatinine clearance < 30 mL/min

ARCOXIA should not be used as adjunctive therapy with other NSAIDs due to the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

[footnote] The Child-Pugh score employs five clinical measures of liver disease - bilirubin, serum albumin, INR, ascites and hepatic encephalopathy. Each measure is scored 1-3, with 3 indicating most severe derangement. The individual scores are tallied to derive the Child-Pugh score.

PRECAUTIONS

Cardiovascular effects

Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with an increased risk of serious thrombotic events (especially MI and stroke), relative to placebo and some NSAIDs. Long term safety data beyond one year are not currently available for etoricoxib compared to placebo or NSAIDs other than diclofenac. In the MEDAL Program, there was no significant difference between etoricoxib and diclofenac in the rate of cardiovascular thrombotic events over a mean treatment duration of 18 months (see CLINICAL TRIALS, *Special Studies).*

As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

A combined analysis of controlled clinical trials in which patients were treated with etoricoxib ≥ 30 mg daily for 4 weeks or longer was conducted to compare the incidence rate of serious thrombotic cardiovascular events among patients taking etoricoxib, placebo, naproxen or non-naproxen NSAIDs. This analysis was not powered to provide a precise estimate of the relative risk of CV events in patients taking etoricoxib versus the other treatments. The analysis showed a statistically significant increase in relative risk with etoricoxib vs naproxen 1000 mg with respect to the Anti-Platelet Trialists' Collaboration (APTC) combined endpoint (ie. cardiovascular, haemorrhagic and unknown death, non-fatal myocardial ischaemia, and non-fatal stroke) [RR 2.72 (95% CI 1.18, 6.27)]. This analysis did not demonstrate any statistically significant increase in the rate of serious thrombotic cardiovascular events in patients taking etoricoxib over those taking non-naproxen NSAIDs (see CLINICAL TRIALS, *Special Studies).*

Etoricoxib should be used with caution for patients with known cardiovascular disease, history of atherosclerotic cardiovascular disease or significant risk factors for cardiovascular events (including those with diabetes, hypertension, hypercholesterolaemia, a first degree relative with ischaemic heart disease, cardiac failure or who are smokers).

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

Aspirin substitution

COX-2 selective inhibitors are not a substitute for aspirin for cardiovascular prophylaxis because of their lack of effect on platelets. Because etoricoxib, a member of this class, does not inhibit platelet aggregation, antiplatelet therapies should not be discontinued.

Gastrointestinal effects

Physicians should be aware that individual patients may develop upper gastrointestinal (GI) ulcers/ulcer complications irrespective of treatment. Although the risk of upper GI toxicity is not eliminated with ARCOXIA, the results of the MEDAL Program demonstrate that in patients treated with ARCOXIA, the risk of upper GI toxicity with ARCOXIA 60 mg or 90 mg once daily is significantly less than with diclofenac 150 mg daily (see CLINICAL TRIALS, *Special Studies*).

In clinical studies with ibuprofen and naproxen, the risk of endoscopically detected upper GI ulcers was lower in patients treated with ARCOXIA 120 mg once daily than in patients treated with the non-selective NSAIDs. While the risk of endoscopically detected ulcers was low in patients treated with ARCOXIA 120 mg it was higher than in patients treated with placebo. Upper GI ulcers/ulcer complications have occurred in patients treated with ARCOXIA. These events can occur at any time during use and without warning symptoms. Independent of treatment, patients with a prior history of GI perforation, ulcers and bleeding (PUB) and patients greater than 65 years of age are known to be at a higher risk for a PUB.

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.

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) when etoricoxib is taken concomitantly with acetylsalicylic acid (even at low doses). A significant difference in GI safety between selective COX-2 inhibitors + acetylsalicylic acid vs NSAIDs + acetylsalicylic acid has not been demonstrated in long-term clinical trials.

Renal effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of ARCOXIA may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Monitoring of renal function in such patients should be considered.

Caution should be used when initiating treatment with ARCOXIA in patients with considerable dehydration. It is advisable to rehydrate patients prior to starting therapy with ARCOXIA.

Fluid retention, oedema, hypertension

As with other drugs known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in patients taking ARCOXIA. All Non-steroidal Anti-inflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. For information regarding a dose related response for etoricoxib, see ADVERSE EFFECTS.

Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with pre-existing oedema from any other reason. If there is clinical evidence of deterioration in the condition of these patients, appropriate measures including discontinuation of etoricoxib should be taken.

Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, hypertension should be controlled before treatment with etoricoxib (see CONTRAINDICATIONS) and special attention should be paid to blood pressure monitoring during treatment with etoricoxib. Blood pressure should be monitored within two weeks after initiation of treatment and periodically thereafter. If blood pressure rises significantly, alternative treatment should be considered.

Hepatic effects

As with other NSAIDs, elevations of one or more liver function tests may occur in up to 15% of patients. Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials treated for up to one year with ARCOXIA 30, 60 and 90 mg daily. In active comparator portions of clinical trials, the incidence of elevated AST and/or ALT in patients treated with ARCOXIA 60 and 90 mg daily was similar to that of patients treated with naproxen 1000 mg daily, but notably less than the incidence in the diclofenac 150 mg daily group. These abnormalities may progress, may remain essentially unchanged, or may resolve in patients with continued treatment of ARCOXIA, with approximately half resolving while patients remained on therapy. In controlled clinical trials of ARCOXIA 30 mg daily versus ibuprofen 2400 mg daily or celecoxib 200 mg daily, the incidence of elevations of ALT or AST was similar.

In post-marketing experience jaundice has been reported rarely. Limited reports of hepatic failure have been reported, but without clear association to ARCOXIA. Physicians 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, pruritus, jaundice abdominal tenderness in the right upper quadrant and "flu-like" symptoms), or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If signs of hepatic insufficiency occur, or if persistently abnormal liver function tests (three times the upper limit of normal) are detected, ARCOXIA should be discontinued.

General

When using etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction, medically appropriate supervision should be maintained. If these patients deteriorate during treatment, appropriate measures should be taken, including discontinuation of therapy.

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 NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance (see ADVERSE EFFECTS). These serious events may occur without warning. Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving etoricoxib (see ADVERSE EFFECTS). Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Use in patients with Inflammatory Bowel Disease (IBD)

NSAIDs have been associated with an exacerbation of IBD associated with spondyloarthropathies. There has only been limited study of etoricoxib in patients with IBD.

Use in patients with fever and infection

ARCOXIA may mask fever, which is a sign of infection. The physician should be aware of this when using ARCOXIA in patients being treated for infection.

Effects on ability to drive and operate machinery

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

Effects on fertility

Etoricoxib administered to male rats at oral doses up to 100 mg/kg/day (systemic exposure about 4-fold greater than that in humans at the maximum recommended dose of 120 mg/day, based on $AUC_{0\text{-}24h}$) had no effects on mating performance, fertility, testicular/epididymal weights, or histology, or sperm count and motility. Etoricoxib produced post-implantation losses in female rats at oral doses of 30 mg/kg/day (approximately 3-fold human exposure at 120 mg daily based on the $AUC_{0\text{-}24hr}$). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function (see PRECAUTIONS, *Use in pregnancy*).

Use in pregnancy

> ***Category C*** *Medicines which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.*

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosis, foetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. Data from epidemiological studies suggest an increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy.

There are no adequate and well-controlled studies of ARCOXIA in pregnant women. ARCOXIA should not be used during the first two trimesters of pregnancy unless the potential benefit justifies the potential risk to the foetus. As with other agents that inhibit prostaglandin synthesis,

treatment with etoricoxib during the third trimester should be avoided because it may cause closure of the foetal ductus arteriosus.

High placental transfer of etoricoxib has been demonstrated in pregnant rats and rabbits. Etoricoxib treatment at oral doses ≥ 30 mg/kg/day prior to or during gestation in pregnant rats or rabbits caused an increase in embryofetal resorptions and reduced the number of foetuses. Exposure to etoricoxib at the no-effect dose for increased resorption (10 mg/kg/day in either species) was lower than that expected in humans after 120 mg, based on AUC. Etoricoxib was not teratogenic in rats at oral doses of 45 mg/kg/day (approximately 4-fold the expected human exposure at a dose of 120 mg/day, based on AUC). A low incidence of ventricular septal defects and other cardiovascular malformations has been observed in rabbits given etoricoxib at oral doses producing exposure levels comparable to that expected in humans. Increased post-natal pup mortality with etoricoxib was observed at doses of 15 and 45 mg/kg/day in rats. Maternal drug exposure at the no-effect dose for increased pup mortality (5 mg/kg/day) was lower than human exposure at a dose of 120 mg/day, based on AUC. In addition, reduced pup weights were observed after oral treatment of pregnant rats with etoricoxib doses of 45 mg/kg/day during gestation and lactation.

Use in lactation

Etoricoxib is excreted in the milk of lactating rats at concentrations up to two-fold greater than the maximal maternal plasma concentration. Because many drugs are excreted in human milk and because of the possible adverse effects of drugs that inhibit prostaglandin synthesis on nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric use

The pharmacokinetics of etoricoxib in paediatric patients (< 12 years of age) have not been studied.

The pharmacokinetics in adolescents (aged 12 to 17) weighing 40 to 60 kg given etoricoxib 60 mg once daily and in adolescents > 60kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily.

Safety and effectiveness in patients aged below 18 years have not been established.

Use in the elderly

Of the 4,562 patients who received ARCOXIA in Phase IIb/III placebo-controlled clinical trials of at least 6 weeks duration, 1,370 were 65 years of age or older (this included 328 who were 75 years or older). Of the 17,412 patients who received ARCOXIA in the MEDAL Program, 7,234 were 65 years of age or older (this included 2,033 patients who were 75 years or older). In each of these datasets, a higher incidence of adverse events was seen in older patients compared to younger patients; the relative differences between the etoricoxib and control groups were similar in the elderly and the young. Greater sensitivity of some older individuals cannot be ruled out. As with any NSAID, caution should be exercised in treating the elderly (65 years and older).

Genotoxicity

Etoricoxib was not genotoxic in assays for gene mutations (*in vitro* bacterial and human lymphoblast [TK locus] cell assays), chromosomal damage (CHO cells *in vitro*, rat bone marrow *in vivo*) and other genotoxic effects (alkaline elution assay of DNA damage *in vitro* and *in vivo*, DNA adduct formation *in vitro*).

Carcinogenicity

When etoricoxib at doses ≥ 30 mg/kg/day (> 6 times the daily human dose [90 mg]) was administered orally for up to 2 years in rats, liver adenomas were observed in the males and females and thyroid follicular cell adenomas were observed in the males, as well. At the lower dose tested in this species (10 mg/kg/day), hepatic cell and thyroid follicular cell hypertrophy were observed in both sexes, and were associated with systemic exposure (AUC_{0-24h}) lower than that expected in humans at the maximum recommended dose of 120 mg.

Etoricoxib was not carcinogenic in mice given oral doses up to 400 mg/kg/day for males and up to 600 mg/kg/day for females for two years. Systemic exposure (AUC_{0-24h}) at these dose levels was similar to that in humans at the maximum recommended dose of 120 mg.

Effects on laboratory tests

Please refer to PRECAUTIONS, *Hepatic effects*, above.

INTERACTIONS WITH OTHER MEDICINES

General: Etoricoxib is an inhibitor of human sulfotransferase activity, particularly SULT1E1 and has been shown to increase the serum concentrations of ethinyl oestradiol (see INTERACTIONS WITH OTHER MEDICINES, *Oral Contraceptives*).

Diuretics, Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin II Antagonists (AIIAs): Reports suggest that NSAIDs including selective COX-2 inhibitors may diminish the antihypertensive effect of diuretics, ACE inhibitors and AIIAs. This interaction should be given consideration in patients taking ARCOXIA concomitantly with these products.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective COX-2 inhibitors, the co-administration of ACE inhibitors or AIIAs may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution, especially in the elderly.

Aspirin: ARCOXIA can be used concomitantly with low-dose aspirin at doses for cardiovascular prophylaxis. At steady state, ARCOXIA 120 mg once daily had no effect on the anti-platelet activity of low-dose aspirin (81 mg once daily), as assessed by *ex vivo* platelet aggregation and serum TXB_2 generation in clotting blood. However, concomitant administration of low-dose aspirin with ARCOXIA increases the rate of GI ulceration or other complications, compared to use of ARCOXIA alone.

Digoxin: ARCOXIA 120 mg once daily for 10 days did not alter the steady state plasma AUC_{0-24hr} or renal elimination of digoxin. Therefore, digoxin and ARCOXIA may be co-administered without dose adjustment.

Frusemide: Clinical studies 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.

Ketoconazole: Ketoconazole, a potent inhibitor of CYP3A4, dosed at 400 mg once a day increased the AUC of etoricoxib by 43%. The clinical significance of this increase is not known.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus, when ARCOXIA and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: Two studies investigated the effects of ARCOXIA 60, 90 or 120 mg administered once daily for seven days in patients receiving once-weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. ARCOXIA at 60 and 90 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In one study, ARCOXIA 120 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In the other study, ARCOXIA 120 mg increased methotrexate plasma concentrations by 28% (as measured by AUC) and reduced renal clearance of methotrexate by 13%. In these two studies, at 24 hours post-dose, a similar proportion of patients treated with methotrexate alone (approximately 93%) and subsequently treated with methotrexate co-administered with ARCOXIA 120 mg (approximately 82%) had methotrexate plasma concentrations below the measurable limit (5 ng/mL). Standard monitoring for methotrexate-related toxicity should be considered when ARCOXIA at doses greater than 90 mg daily and methotrexate are administered concomitantly.

Oral Contraceptives: ARCOXIA 60 mg given concomitantly with an oral contraceptive containing 35mcg ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state $AUC_{0\text{-}24hr}$ of EE by 37%. ARCOXIA 120 mg given with the same oral contraceptive, concomitantly or separated by 12 hours, increased the steady state $AUC_{0\text{-}24hr}$ of EE by 50 to 60%. This increase in EE concentration should be considered when selecting an oral contraceptive for use with ARCOXIA. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g. venous thromboembolic events in women at risk).

Hormone Replacement Therapy: Administration of ARCOXIA 120 mg with hormone replacement therapy consisting of conjugated oestrogens (0.625 mg PREMARIN™) for 28 days, increased the mean steady state $AUC_{0\text{-}24hr}$ of unconjugated estrone (41%), equilin (76%), and 17-β-oestradiol (22%). The effect of the recommended chronic doses of ARCOXIA (30 and 60 mg) has not been studied. The effects of ARCOXIA 120 mg on the exposure ($AUC_{0\text{-}24}$) to these oestrogenic components of PREMARIN were less than half of those observed when PREMARIN was administered alone and the dose was increased from 0.625 to 1.25 mg. The clinical significance of these increases is unknown, and higher doses of PREMARIN were not studied in combination with ARCOXIA. These increases in oestrogenic concentration should be taken into consideration when selecting post-menopausal hormone replacement therapy for use with ARCOXIA.

Prednisone/prednisolone: Etoricoxib did not have any clinically important effect on the pharmacokinetics of prednisolone or prednisone.

Rifampicin: Co-administration of ARCOXIA with rifampicin, a potent inducer of hepatic metabolism, 600 mg daily, produced a 65% decrease in etoricoxib plasma AUC. This interaction should be taken into consideration when ARCOXIA is co-administered with rifampicin.

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing ARCOXIA therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. In a multiple dose study in healthy subjects receiving both warfarin and ARCOXIA 120 mg, the steady state prothrombin time (measured as INR) was increased by approximately 13%.

ADVERSE EFFECTS

In ten Phase IIb/III placebo-controlled clinical trials of at least 6 weeks duration for OA, 1,572 patients were treated with ARCOXIA 30 mg or 60 mg; 563 patients received ARCOXIA for up to one year.

In the 6 to 12 week placebo-controlled population, discontinuations due to clinical adverse experiences for ARCOXIA 30 mg, ARCOXIA 60 mg, and placebo were 4.3%, 5.0%, and 6.1 %. The most common reasons for discontinuation due to adverse experiences in OA patients treated with ARCOXIA, 30 and 60 mg, were dyspepsia and dizziness (0.4% and 0.4% of patients, respectively). Among patients receiving placebo, 0.3% discontinued due to dyspepsia and 0.1% due to dizziness (see also Table 6).

In patients treated for up to one year, discontinuations due to clinical adverse experiences for ARCOXIA 30 mg, ARCOXIA 60 mg, and naproxen were 7.3%, 12.6%, and 18.7% respectively. The most common reasons for discontinuation due to adverse experiences in patients treated with ARCOXIA 30 and 60 mg, were dyspepsia and upper abdominal pain (0.9% and 1.1% respectively); in patients treated with naproxen, discontinuations due to dyspepsia and upper abdominal pain were 1.6% and 2.3% respectively.

In three Phase IIb/III placebo-controlled studies for rheumatoid arthritis of at least 6 weeks duration, 810 patients were treated with ARCOXIA 90 mg; 467 patients were treated with ARCOXIA 90 mg for up to one year.

In the 6 to 12 week RA population, discontinuations due to clinical adverse experiences were 3.5% for ARCOXIA 90 mg and 2.9% for placebo. The most common causes of discontinuation were dyspnoea, breast malignant neoplasm and headache with each event occurring at 0.2% in patients treated with ARCOXIA. In the placebo group, 0% of patients discontinued due to dyspnoea and breast malignant neoplasm; 0.4% due to headache.

In RA patients treated for up to one year, discontinuations due to clinical adverse experiences were 7.5% for ARCOXIA 90 mg and 10.5% for naproxen. The most common causes of discontinuation in patients treated with ARCOXIA were dyspepsia (0.6%) and heartburn (0.6%). In the naproxen group, 1.1% and 0.9% of patients discontinued due to dyspepsia and to heartburn, respectively.

In the MEDAL Study, an endpoint driven CV outcomes trial involving 23,504 patients, the safety of ARCOXIA 60 or 90 mg daily was compared to diclofenac 150 mg daily in patients with OA or RA (mean duration of treatment was 20 months) (see ADVERSE EFFECTS, *Additional Safety Data from the MEDAL Program Studies*, below).

In two placebo-controlled clinical trials of 12 weeks duration for chronic low back pain, 425 patients were treated with ARCOXIA 60 mg or 90 mg daily. Discontinuations due to clinical adverse experiences were reported in ARCOXIA 60 mg (11.3%), ARCOXIA 90 mg (10.8%), and placebo (7.3 %). The most common causes of discontinuation were asthenia/fatigue, back

strain, and rash with each event occurring at 0.7% in patients treated with ARCOXIA. In the placebo group, 0% of patients discontinued due to asthenia/fatigue and back strain; 0.5% due to rash.

In twelve acute analgesia studies, 1,586 patients were treated with ARCOXIA in either a single dose or multiple dose regimen.

In the single dose population, 1,001 patients were treated with ARCOXIA (dosages of 12.5 to 240 mg). Six patients discontinued due to clinical adverse experiences including 0.9% on ARCOXIA (less than 120 mg), 0.5% on placebo, 1.6% on ibuprofen, and 0.3% on naproxen.

In the multiple dose acute analgesia study population, 297 patients received ARCOXIA 120 mg as the initial dose followed by 60 mg or 120 mg once daily for up to 7 days. Discontinuations due to adverse experiences were 8.2%, 5.4%, 4.7%, and 2.7% in the placebo/placebo group, ARCOXIA 120 mg/60 mg group, ARCOXIA 120 mg/120 mg group, and the naproxen/placebo group respectively. The most common causes of discontinuation for those patients treated with ARCOXIA were nausea and confusion. In the post-dental surgery pain study of 191 patients treated with ARCOXIA 90 mg once daily for up to 3 days, the adverse experience profile was generally similar to that reported in patients treated with ARCOXIA 120 mg in all acute analgesia studies.

In two active-comparator clinical trials for acute gouty arthritis, 178 patients were treated with ARCOXIA 120 mg once daily for eight days. Discontinuations due to adverse experiences were 3.9 % and 8.1% in patients treated with ARCOXIA and indomethacin respectively. The most common cause of discontinuation was hypertension occurring at 1.1% and 1.2% of patients treated with ARCOXIA and indomethacin, respectively.

Osteoarthritis

The following table lists all adverse experiences, regardless of causality, occurring in at least 2% of patients receiving ARCOXIA in ten placebo-controlled studies of 6- to 12-weeks duration conducted in patients with OA, at the therapeutically recommended doses (30 mg and 60 mg). Since these ten trials were of different durations, and patients in the trials may not have been exposed for the same duration of time, these percentages do not capture cumulative rates of occurrence.

Table 6 Clinical Adverse Experiences occurring in ≥2.0% of Patients Treated with ARCOXIA in OA Clinical Trials

	Placebo (N = 1035)	*Etoricoxib 30 mg (N=1014)*	*Etoricoxib 60 mg (N = 558)*	*Celecoxib 200 mg (N = 488)*	*Ibuprofen 2400 mg (N = 756)*	*Naproxen 1000 mg (N = 494)*
Infections and infestations						
Nasopharyngitis	*2.3*	*2.1*	*3.2*	*1.4*	*2.8*	*3.8*
Upper Respiratory Tract Infection	*2.2*	*1.9*	*5.9*	*2.3*	*2.2*	*4.0*
Urinary Tract Infection	*1.3*	*2.9*	*2.9*	*2.5*	*2.5*	*2.6*
Nervous system disorders						
Dizziness	*1.1*	*1.6*	*2.2*	*2.7*	*1.3*	*3.4*
Headache	*3.2*	*3.3*	*5.6*	*3.7*	*4.2*	*3.8*
Vascular disorders						
Hypertension	*2.3*	*3.0*	*4.5*	*0.8*	*5.4*	*3.0*
Gastrointestinal disorders						
Abdominal Pain, Upper	*1.4*	*1.4*	*2.0*	*0.8*	*4.6*	*4.7*
Diarrhoea	*3.1*	*3.6*	*3.9*	*2.5*	*4.4*	*4.3*
Dyspepsia	*4.8*	*2.9*	*4.1*	*1.4*	*7.8*	*9.9*
Nausea	*3.1*	*2.2*	*3.0*	*1.8*	*2.9*	*6.3*
General disorders and administration site conditions						
Peripheral Oedema	*1.5*	*2.7*	*2.9*	*2.5*	*3.0*	*2.6*

The following lists additional adverse experiences, regardless of causality, occurring in patients receiving ARCOXIA with a frequency of between 0.1% and less than 2.0% and at least 0.1% more frequently than in the placebo treatment group in ten placebo-controlled studies of 6- to 12-weeks duration conducted in patients with OA at the therapeutically recommended doses (30 mg and 60 mg).

Infections and infestations: herpes simplex, infection, pharyngitis, sinusitis, staphylococcal infection, tonsillitis.

Immune system disorders: seasonal allergy.

Metabolism and nutrition disorders: diabetes mellitus.

Psychiatric disorders: anxiety, anxiety disorder, depression.

Nervous system disorders: carpal tunnel syndrome, paresthesia, somnolence, vasovagal syncope, tremor.

Eye disorders: blepharitis, conjunctivitis, eye pain, vision blurred.

Ear and labyrinth disorders: tinnitus.

Cardiac disorders: palpitations.

Vascular disorders: diastolic hypertension, flushing, hot flush.

Respiratory, thoracic and mediastinal disorders: cough, dyspnoea exertional, rales, sinus congestion, wheezing.

Gastrointestinal disorders: abdominal distension, aphthous stomatitis, bowel sounds abnormal, change of bowel habit, constipation, dry mouth, frequent bowel movements, gastritis, glossitis, irritable bowel syndrome, mouth ulceration, oral pain, retching, toothache.

Skin and subcutaneous tissue disorders: blister, dermal cyst, dermatitis, eczema, hyperhidrosis, rash, rash maculopapular, rosacea, skin ulcer.

Musculoskeletal and connective tissue disorders: neck pain, osteoporosis, periarthritis, rotator cuff syndrome, tendinitis, toe deformity.

Renal and urinary disorders: nephrolithiasis, nocturia, polyuria.

Reproductive system and breast disorders: erectile dysfunction, vaginal haemorrhage.

General disorders and administration site conditions: asthenia, face oedema, fatigue, feeling hot, oedema.

Investigations: faecal occult blood positive.

Injury, poisoning and procedural complications: contusion, foot fracture, joint sprain, skin laceration.

The following list includes additional serious adverse experiences that occurred at a frequency of ≤ 0.1% and in two or more patients in placebo-controlled clinical trials of 6 to 12 weeks duration, or that occurred in two or more patients taking ARCOXIA in active comparator controlled trials of up to 190 weeks, regardless of causality. This listing includes events reported in clinical trials of OA and non-OA indications across a dose range of 30 mg to 120 mg daily. The MEDAL Program data is described separately below.

Infections and infestations: abscess, cellulitis, pneumonia, post operative wound infection, pyelonephritis, sinusitis, staphylococcosis.

Neoplasms benign and unspecified (including cysts and polyps): bladder malignant neoplasm, breast malignant neoplasm, malignant melanoma, non-Hodgkin's lymphoma, uterine fibroid.

Nervous system disorders: cerebrovascular accident, grand mal seizure, intracranial haemorrhage, spinal stenosis, subarachnoid haemorrhage, syncope, transient ischaemic attack.

Cardiac disorders: angina pectoris, arrhythmia, atrial fibrillation, cardiac arrest, coronary artery disease, congestive heart failure, ischaemic heart disease, mitral valve regurgitation, unstable angina.

Vascular disorders: deep venous thrombosis, hypertensive crisis, hypovolemic shock, lacunar infarction.

Respiratory, thoracic and mediastinal disorders: dyspnoea, pulmonary embolism, respiratory insufficiency.

Gastrointestinal disorders: gastroesophageal reflux disease, haemorrhagic gastric ulcer, intestinal diverticulitis, pancreatitis, upper gastrointestinal haemorrhage, vomiting.

Hepatobiliary disorders: cholecystitis, cholelithiasis.

Musculoskeletal and connective tissue disorders: arthralgia, chest pain, hip osteoarthritis, knee osteoarthritis, knee pain, osteoarthritis, rheumatoid arthritis, rotator cuff trauma.

Renal and urinary disorders: renal colic, urolithiasis.

Pregnancy, puerperium and perinatal conditions: pregnancy.

General disorders and administration site conditions: constricted feeling in chest, fever, prolapse.

Injury, poisoning and procedural complications: drug overdose, femoral fracture, hip fracture, humeral fracture, motor vehicle accident, tendon rupture, wrist fracture.

Additional Safety Data from the MEDAL Program Studies

In the MEDAL Study, an endpoint driven CV outcomes trial involving 23,504 patients, the safety of ARCOXIA 60 or 90 mg daily was compared to diclofenac 150 mg daily in patients with OA or RA (mean duration of treatment was 20 months). In this large trial, only serious adverse events and discontinuations due to any adverse events were recorded. The rates of confirmed thrombotic cardiovascular serious adverse events were similar between ARCOXIA and diclofenac. The incidence of discontinuations for hypertension-related adverse events was less than 3% in each treatment group; however, ARCOXIA 60and 90 mg demonstrated significantly higher rates of discontinuations for these events than diclofenac. The incidence of congestive heart failure adverse events (discontinuations and serious events) and the incidence of discontinuations due to oedema occurred at similar rates on ARCOXIA 60 mg compared to diclofenac, however, the incidences for these events were higher for ARCOXIA 90 mg compared to diclofenac (see Table 7). The incidence of discontinuations due to atrial fibrillation was higher for etoricoxib compared to diclofenac (in OA patients: 0.8% versus 0.3 % for etoricoxib 90 mg and diclofenac respectively; 0.3 versus 0.2 for etoricoxib 60 mg versus diclofenac respectively).

Table 7 Pre-specified Adverse Events of Interest by Disease and Dose

	Osteoarthritis 60 mg		**Osteoarthritis 90 mg**		**Rheumatoid Arthritis**	
	Etoricoxib 60 mg (N=6769)	Diclofenac 150 mg (N=6700)	Etoricoxib 90 mg (N=2171)	Diclofenac 150 mg (N=2162)	Etoricoxib 90 mg (N=2841)	Diclofenac 150 mg (N=2855)
Adverse Experience (AE)						
Confirmed congestive heart failure‡	0.28 vs 0.21 (p-Value 0.487)		0.69 vs 0.32 (p-Value 0.133)		0.63 vs 0.32 (p-Value 0.086)	
% of Patients Discontinued due to:						
Oedema-related AEs	0.83 vs 0.73 (p-Value 0.557)		1.89 vs 0.79 (p-Value 0.002)		0.99 vs 0.56 (p-Value 0.071)	
Hypertension-related AEs	2.16 vs 1.63 (p-Value 0.027)		2.53 vs 1.11 (p-Value < 0.001)		2.43 vs 1.61 (p-Value 0.030)	
Hepatic-related AEs	0.33 vs 1.78 (p-Value <0.001)		0.37 vs 4.07 (p-Value <0.001)		0.42 vs 1.68 (p-Value < 0.001)	
Renal-related AEs	0.81 vs 0.75 (p-Value 0.696)		2.30 vs 1.80 (p-Value 0.284)		1.02 vs 0.98 (p-Value 0.895)	
N = total number of patients; p-Values are for the difference between etoricoxib and diclofenac ‡ Confirmed cases of CHF which were serious or resulted in discontinuation from the study and resulted in hospitalisation.						

The EDGE and EDGE II studies compared the GI tolerability of etoricoxib 90 mg daily (1.5 to 3 times the doses recommended for OA) and diclofenac 150 mg daily in 7,111 patients with OA (EDGE Study; mean duration of treatment 9 months) and 4,086 patients with RA (EDGE II; mean duration of treatment 19 months). In each of these studies, the adverse experience profile on ARCOXIA was generally similar to that reported in the Phase IIb/III placebo-controlled clinical studies; however, hypertension and oedema-related adverse events occurred at a higher

rate on etoricoxib than on diclofenac. The rate of confirmed thrombotic cardiovascular serious adverse events occurring in the two treatment groups was similar.

Acute Pain, including Primary Dysmenorrhoea

Approximately 1,088 patients were treated with ARCOXIA 90mg or 120 mg in acute analgesia studies. Patients in primary dysmenorrhoea and dental pain studies may have taken up to three daily doses of ARCOXIA, and those in the post-orthopaedic surgery pain study were prescribed seven daily doses of ARCOXIA.

The adverse experience profile in the acute analgesia studies was generally similar to that reported in the combined OA, RA, and chronic low back pain studies. The following additional adverse events, which occurred at an incidence of at least 2% of patients treated with ARCOXIA, were observed in the post-dental pain surgery and primary dysmenorrhoea studies: dysgeusia, post-dental extraction alveolitis (dry socket).

In the 161 patients treated with ARCOXIA (average age approximately 65 years) in the post-orthopaedic surgery pain study, the most commonly reported adverse events were constipation, insomnia, and nausea.

Acute Gouty Arthritis

In clinical studies for acute gouty arthritis, patients were treated with ARCOXIA 120 mg once daily for eight days. The adverse experience profile in these studies was generally similar to that reported in the combined OA, RA, and chronic low back pain studies. The most commonly reported adverse events in patients treated with ARCOXIA 120 mg (N=178) were gout, dizziness, and hypertension at 11.2%, 3.4%, and 7.9% respectively. In patients treated with indomethacin 150 mg daily (N=161), gout, dizziness, and hypertension were observed at 8.7%, 16.1%, and 9.9% respectively.

Rheumatoid Arthritis, Chronic Low Back Pain – Non-approved indications

In clinical studies for rheumatoid arthritis, 810 patients were treated with ARCOXIA 90 mg daily for 6 to 12 weeks. The most commonly observed adverse events in these patients were upper respiratory infection, diarrhoea, and headache.

In clinical studies for rheumatoid arthritis, 467 patients were treated with ARCOXIA 90 mg daily for up to one year. The most commonly observed adverse events in these patients were upper respiratory infection, urinary tract infection, hypertension and headache.

In clinical studies for chronic low back pain, 425 patients were treated with ARCOXIA 60 mg or 90 mg for 12 weeks. The most commonly observed adverse events in these patients were diarrhoea, nausea and headache.

Post-marketing experience

The following adverse reactions have been observed in post-marketing experience:

Psychiatric disorders: insomnia, confusion, hallucinations, depression, restlessness.

Immune system disorders: hypersensitivity reactions, anaphylactic/anaphylactoid reactions including shock.

Metabolism and nutrition disorders: hyperkalaemia.

Nervous system disorders: dysgeusia, somnolence.

Cardiac disorders: congestive heart failure, palpitations, angina, arrhythmia.

Respiratory, thoracic and mediastinal disorders: bronchospasm, dyspnoea.

Gastrointestinal disorders: abdominal pain, melaena, oral ulcers, peptic ulcers including perforation and bleeding (mainly in elderly patients).

Skin and subcutaneous tissue disorders: angioedema, rash, pruritus, erythema, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, fixed drug eruption.

Renal and urinary disorders: renal insufficiency, including renal failure (see PRECAUTIONS)

Hepatobiliary disorders: hepatitis, jaundice, hepatic failure.

Blood and lymphatic system disorders: thrombocytopenia.

The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome, hepatotoxicity and pancreatitis.

DOSAGE AND ADMINISTRATION

ARCOXIA is administered orally. ARCOXIA may be taken with or without food.

As the cardiovascular risks of etoricoxib may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. Patients on long term treatment should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment..

Osteoarthritis

The recommended dose is 30 mg once daily. In some patients with insufficient relief from symptoms, the dose may be increased to 60 mg once daily. In the absence of therapeutic benefit after 4 weeks of treatment with etoricoxib 60 mg, other therapeutic options should be considered.

In the following acute painful conditions:

Acute Gouty Arthritis

The recommended dose is 120 mg once daily.

ARCOXIA should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.

Primary Dysmenorrhoea

The recommended dose is 120 mg once daily.

ARCOXIA should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.

Dental Pain

The recommended dose is 90 mg once daily.

ARCOXIA should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.

Doses greater than those recommended for each indication have either not demonstrated additional efficacy or have not been studied. Therefore:

The dose for OA should not exceed 60 mg daily.

The dose for acute pain, primary dysmenorrhoea, and acute gout should not exceed 120 mg daily, limited to a maximum of 8 days treatment.

The dose for dental pain should not exceed 90 mg, limited to a maximum of 8 days treatment.

Hepatic Insufficiency

In patients with mild hepatic insufficiency (Child-Pugh score 5-6), a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic insufficiency (Child-Pugh score 7-9), the dose should be reduced; a dose of 60 mg ***every other day*** should not be exceeded, administration with 30 mg once daily can also be considered. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score > 9) (see CONTRAINDICATIONS and PRECAUTIONS).

Renal Insufficiency

In patients with advanced renal disease (creatinine clearance <30 mL/min), treatment with ARCOXIA is not recommended. No dosage adjustment is necessary for patients with lesser degrees of renal insufficiency (creatinine clearance ≥30 mL/min) (see PRECAUTIONS).

Elderly, Gender, Race

No dosage adjustment in ARCOXIA is necessary for the elderly or based on gender or race.

OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or 0800 764 766 (New Zealand).

In clinical studies, administration of ARCOXIA at single doses up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity. There have been reports of acute overdosage with etoricoxib, although adverse events were not reported in the majority of cases. The most frequently observed adverse events were consistent with the safety profile for etoricoxib (e.g. gastrointestinal events, renovascular events).

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., employ clinical monitoring, and institute supportive therapy, if required.

Etoricoxib is not dialysable by haemodialysis; it is not known whether etoricoxib is dialysable by peritoneal dialysis.

PRESENTATION AND STORAGE CONDITIONS

ARCOXIA (etoricoxib) 30 mg is a blue-green, apple-shaped, biconvex film coated tablet debossed ”101” on one side and ”ACX 30” on the other side. Available in PA/Aluminium-PVC/Aluminium blister packs of 5 tablets[#], 10 tablets (starter pack) [#] and 30 tablets.

ARCOXIA (etoricoxib) 60 mg is a dark green, apple-shaped, biconvex film coated tablet engraved ”200” on one side and ”ARCOXIA 60” on the other side. Available in PA/Aluminium-PVC/Aluminium blister packs of 5 tablets[#], 10 tablets[#], and 30 tablets.

ARCOXIA (etoricoxib) 90mg is a white, apple-shaped, biconvex film coated tablet debossed "202" on one side and "ARCOXIA 90" on the other side. Available in PA/Aluminium-PVC/Aluminium blister packs of 2 tablets[#] (starter pack), 5 tablets[#], and 10 tablets[#].

ARCOXIA (etoricoxib) 120 mg is a pale green, apple-shaped, biconvex film coated tablet engraved ”204” on one side and ”ARCOXIA 120” on the other side. Available in PA/Aluminium-PVC/Aluminium blister packs of 2 tablets (starter pack)[#], 5 tablets[#], and 10 tablets.

[#]*Presentation not currently marketed in Australia.*

ARCOXIA Tablets should be stored below 30ºC. Store in the original package.

NAME AND ADDRESS OF THE SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited

Level 1, Building A, 26 Talavera Road, Macquarie Park, NSW 2113

POISON SCHEDULE OF THE MEDICINE: Prescription only medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 11 October 2002

DATE OF MOST RECENT AMENDMENT: 14 July 2017

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