JPP Journal of Pharmacy and Pharmacology

JPP 2003, 55: 859–894

Received September 27, 2002
Accepted April 17, 2003
DOI 10.1211/0022357021387
ISSN 0022-3573

Review Article

Rofecoxib: an update on physicochemical, pharmaceutical, pharmacodynamic and pharmacokinetic aspects

Naveen Ahuja, Amarjit Singh and Bhupinder Singh

Abstract

Rofecoxib (MK-966) is a new generation non-steroidal anti-inflammatory agent (NSAID) that exhibits promising anti-inflammatory, analgesic and antipyretic activity. It selectively inhibits cyclooxygenase (COX)-2 isoenzyme in a dose-dependent manner in man. No significant inhibition of COX-1 is observed with rofecoxib up to doses of 1000 mg. The pharmacokinetics of rofecoxib has been found to be complex and variable. Mean oral bioavailability after single dose of rofecoxib (12.5, 25 or 50 mg) is 93% with t_{max} varying widely between 2 and 9 h. It is highly plasma-protein bound and is metabolized primarily by cytosolic reductases to inactive metabolites. Rofecoxib is eliminated predominantly by hepatic metabolism with a terminal half-life of approximately 17 h during steady state. Various experimental models and clinical studies have demonstrated rofecoxib to be superior, or at least equivalent, in anti-inflammatory, analgesic and antipyretic efficacy to comparator non-selective NSAIDs in osteoarthritis, rheumatoid arthritis and other pain models. Emerging evidence suggests that rofecoxib may also find potential use as supportive therapy in various pathophysiologic conditions like Alzheimer's disease, and in various malignant tumours and polyps, where COX-2 is overly expressed. Rofecoxib is generally well-tolerated. Analysis of data pooled from several trials suggests that rofecoxib is associated with fewer incidences of clinically symptomatic gastrointestinal ulcers and ulcer complications vis-à-vis conventional NSAIDs. However, this gastropreserving effect may be negated by concurrent use of low-dose aspirin for cardiovascular risk reduction. Rofecoxib tends to show similar tolerability for renal and cardiothrombotic events as compared with non-naproxen nonselective NSAIDs. No clinically significant drug interaction has been reported for rofecoxib except with diuretics, where it reverses their salt-wasting effect and thus can be clinically exploited in electrolyte-wasting disorders. There is only modest information about the physicochemical and pharmaceutical aspects of rofecoxib. Being poorly water soluble, its drug delivery has been improved using varied formulation approaches. Although it is stable in solid state, rofecoxib is photosensitive and base-sensitive in solution form with its degradation mechanistics elucidated. Analytical determinations of rofecoxib and its metabolites in biological fluids employing HPLC with varied types of detectors have been reported. Isolated studies have also been published on the chromatographic and spectrophotometric assay of rofecoxib and its degradants in bulk samples and pharmaceutical dosage forms. The current article provides an updated overview on the physicochemical, pharmaceutical, pharmacokinetic and pharmacodynamic vistas of rofecoxib.

University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh 160 014 India

Naveen Ahuja, Bhupinder Singh

Pharma Research and Development, Panacea Biotec Ltd., P.O. Lalru, Punjab 140 501, India

Amarjit Singh

Correspondence: B. Singh, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh 160 014, India. E-mail: bsbhoop@yahoo.com; bsbhoop@rediffmail.com

Funding: We thank M/s Panacea Biotec Ltd (New Delhi, India), for financially supporting this project and providing research associateship to one of us (N. A.).

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most frequently prescribed group of drugs worldwide. They are highly effective as analgesics, antipyretics and anti-inflammatory agents (Brooks & Day 2000). Although generally safe, they account for nearly one-fourth of all reported adverse drug events (Noble et al 2000). They have been held responsible for substantial morbidity and mortality as a result of gastrointestinal complications like perforation and bleeding associated with gastroduodenal ulcers (Roth 1986; Fries 1991; Hawkey et al 2000). The therapeutic efficacy as well as toxicity of NSAIDs is generally attributed to the blockade of prostaglandin synthesis by inhibition of cyclooxygenase (COX) enzymes (Vane 1971; Chan et al 1999).

COX is a bifunctional membrane-bound haemoprotein also known as prostaglandin endoperoxide synthase (Chan et al 1999). It catalyzes the transformation of arachidonic acid to cyclic endoperoxide by bisoxygenation. The latter serves as the common precursor for the synthesis of prostaglandins, prostacyclin and thromboxanes (Figure 1), collectively known as prostanoids (Jackson & Hawkey 2000). Two COX isoforms have been identified and characterized (Vane & Botting 1995; Smith & DeWitt 1996). A largely constitutive form is termed COX-1, while a largely inducible form is COX-2. These two isoforms have similar active sites and catalytic properties, but are structurally distinct with only about 60% amino-acid homology (Smith et al 1996; Griswold & Adams 1996). Expression of COX-1 is ubiquitous and its activity predominates during normal physiologic conditions. COX-1 is known to be a housekeeping enzyme that generates prostaglandins responsible for protection of gastric mucosal lining, regulation of blood flow to kidney and supporting platelet aggregation. It is only slightly upregulated in some cells in response to hormones or growth factors (DeWitt 1991; Noble et al 2000). COX-2 is constitutively present in brain (Kaufman et al 1996), reproductive tract (Lim et al 1997), renal cortex (Kömhoff et al 1997) and pancreatic islet cells (Robertson 1998). It is markedly upregulated in response to inflammatory cytokines or other stressors (Akaraserennont et al 1994; Mitchell et al 1994; Vadas et al 1996). These distinct expression patterns have led to the proposal that prostaglandins produced by COX-1 are largely responsible for physiologic function (Meade et al 1993), while COX-2-derived prostaglandins mediate pathophysiologic and inflammatory processes.

Traditional NSAIDs owe their therapeutic benefits to the inhibition of COX-2, whereas their side-effect profile is due to inhibition of COX-1 (Jackson & Hawkey 2000; Brune & Neubert 2001). Their spectrum of activity against COX ranges from a selectivity toward COX-1 to an equiselectivity for both COX-1 and COX-2. In an attempt to overcome the toxicity of conventional NSAIDs, drug molecules like meloxicam, nimesulide, etodolac, nabumetone, etc., attained greater popularity owing to their relative preferential inhibition of COX-2 and consequently somewhat better gastrointestinal tolerability (Hawkey 1999; Rehman & Sack 1999; Singla et al 2000). However, there is always a risk of loss of selectivity for COX-2 at higher doses of these inhibitors thus proving to be no better than nonselective NSAIDs at higher doses. A newer class of anti-inflammatory agents (selective COX-2 inhibitors — coxibs) has been gaining increased attention in clinical practice lately (Pasucucci 1999; Jackson & Hawkey 2000; FitzGerald & Patrono 2001; FitzGerald et al 2001). This class has purely emerged from the drug development programmes based upon the structural differences between COX-1 and COX-2 so that the problem of loss of selectivity at higher doses is minimized. In general, coxibs are said to have an efficacy profile similar to

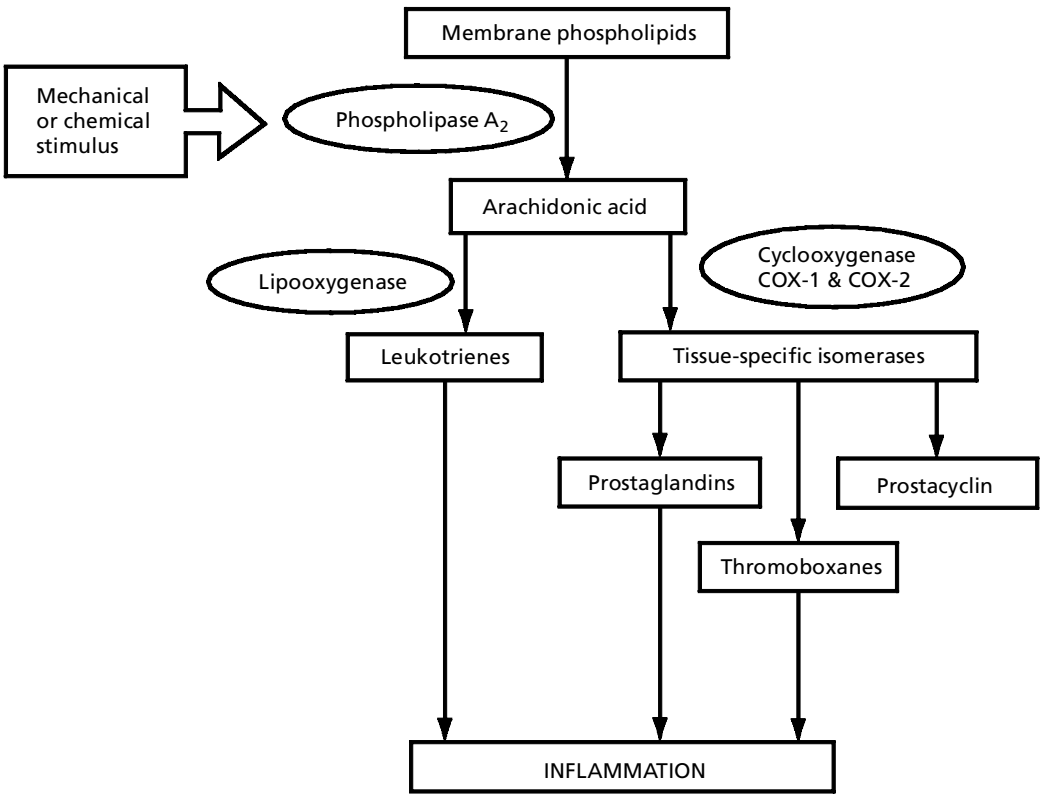


Figure 1 Arachidonic acid cascade.

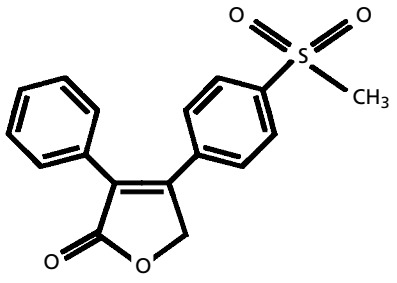
that of conventional NSAIDs, but with better gastrointestinal tolerability (Simon 2001; Steinfeld & Poriau 2001; Bingham 2002). Therefore, the higher popularity of coxibs vis-à-vis traditional NSAIDs is not related to any increased efficacy in treating pain or inflammation, but to their more favourable gastrointestinal tolerability.

Rofecoxib (MK-966) is a specific COX-2 NSAID approved by the US FDA on 21 May 1999 for the relief of the signs and symptoms of osteoarthritis (OA), management of acute pain in adults, and in the treatment of primary dysmenorrhoea (Merck & Co. 1998; FDA 1999a; Kaplan-Machlis & Klostermeyer 1999; Scheen 2000). Very recently, on 11 April 2002, the US FDA granted approval for the use of rofecoxib in rheumatoid arthritis (FDA 2002a).

Physicochemical aspects

Chemically, rofecoxib is a methyl sulphonyl phenyl derivative (Figure 2) with the molecular formula of $C_{17}H_{14}O_4S$ and molecular weight of 314.36 (Merck & Co. 1998). Forgione et al (2000) reported a method of synthesis of rofecoxib starting from phenylpropargyl alcohol. Thérien et al (2001) also described a method for the chemical synthesis of rofecoxib starting from Freidal-Craft acylation of thioanisole. The sequences of the principal steps involved in both of these synthetic procedures are portrayed in Figure 3. Recently, Wu et al (2002) also described another procedure to synthesize rofecoxib starting from 4-(methylsulphonyl) acetophenone and phenylacetic acid, reporting the yield of the drug as 64%.

Rekha et al (2000) and recently, Kiang et al (2003) have elucidated the crystal structure of rofecoxib through X-ray diffractometery. While the former adopted studies using a single-crystal method, the latter extensively investigated the powder sample using molecular-packing analysis and direct-space methods. Although the correct rofecoxib crystal structure was obtained by direct-space method using a molecular model with standard S–C and S═O distances, the results were remarkably similar in all the studies. The scientists concluded from the X-ray diffractograms that only van der Waals interactions are present between the drug molecules (Kiang et al 2003).



4-[4-(Methylsulphonyl)phenyl]-3-phenyl-2(5*H*)-furanone

Figure 2 Chemical structure of rofecoxib.

Rofecoxib is a white to off-white to light-yellow powder with melting point of 204–208 °C (Merck & Co. 1998). It is sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol, practically insoluble in octanol and insoluble in water. It is known to exist only in one polymorphic form (Kiang et al 2003). Various spectral characteristics of the drug reported in literature (Thérien et al 2001; Reddy et al 2002) are depicted in Table 1.

Hardly any report has been published on the pK_a and lipophilicity of this compound. Nevertheless, the value of log P computed theoretically using Pallas software (Version 2.0, CompuDrug Limited, 1996) was found to be 2.14 (Singh et al 2003). However, the software failed to compute the pK_a value of the drug indicating that there are no acidic and basic moieties detectable in the molecule. The value of log P obtained from chemical databases provided by American Chemical Society, however, is 1.635.

Pharmaceutical aspects

Formulation

Being a poorly water-soluble drug, the development of rofecoxib formulation(s) is an exigent task. The aqueous solubility of rofecoxib has been enhanced by methods such as the formation of inclusion complexes with β-cyclodextrin (Aristo Pharmaceuticals Limited, 2000), formulation of porous drug matrices (Straub et al 2002), and dispersions with various solubility-enhancing carriers like hydrotropes, poloxamers and Gelucire 44/14 (Singh et al 2003). Improved drug delivery can also be achieved by formulating rofecoxib into a clear oil preparation using excipients like Cremophor RH-40, Crovol M-40 and corn oil (Chen & Patel 2001), or by incorporating the drug into a carrier that is a blend of hydrophilic and hydrophobic surfactants (Patel & Chen 2001). Further, there have been studies (Murpani & Malik 2002; Karali et al 2002) connoting the attainment of immediate release of the drug by formulation of its oral fast-melt tablets. The enhanced delivery of rofecoxib through topical or transdermal routes has been obtained employing either a penetration-enhancing base (containing dimethyl sulfoxide) or penetration enhancers like β-cyclodextrin or Brij 30 (Singh & Jain 2001; Selzer 2002; Wockhardt 2002). Hirsh et al (2002) have formulated a multi-layered unit dosage form of rofecoxib for both intraoral and oral administration. The formulation provides two doses of analgesic, one for immediate release and the other for delayed release. Microemulsions of rofecoxib have been prepared using triglycerides, fatty acids and surfactants (Supersaxo et al 2002). Further, an oral osmotic drug delivery device, containing rofecoxib along with the centrally acting analgesic tramadol, has also been formulated (Faour & Coppari 2001).

Stability

Rofecoxib is reported to be stable in solid state under exposure conditions as proposed by ICH light (Mao et al 2002). However in solution form, the drug is sensitive to

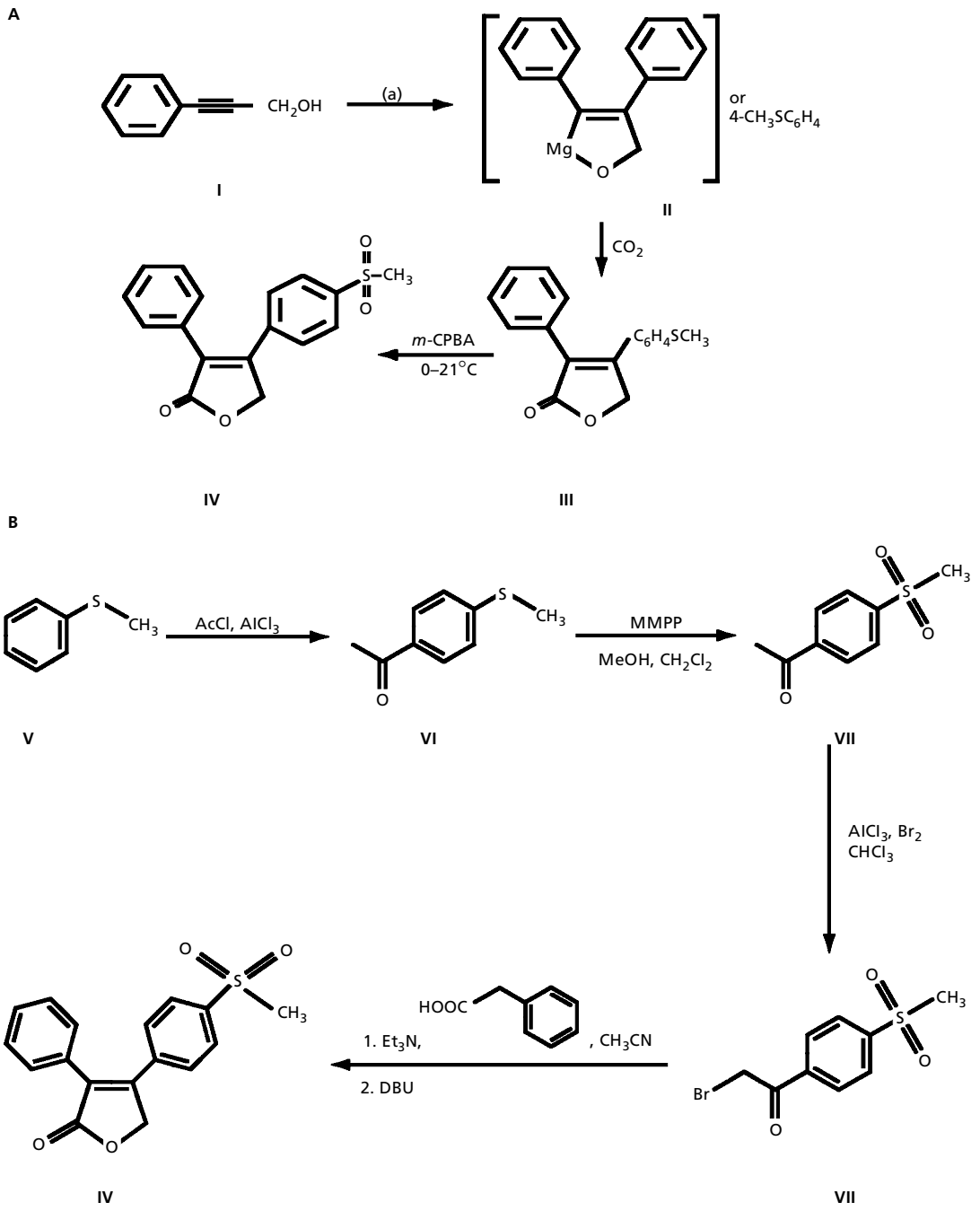


Figure 3 The major chemical steps involved in the synthesis of rofecoxib. A. Synthesis starting from phenylpropargyl alcohol (I); II: magnesium chelate; III: 4-[4-(methylthio)phenyl]-3-phenyl-2(5H)-furanone; IV: rofecoxib; (a): 3.2 equivalent phenyl magnesium chloride or 4-thiomethylphenylmagnesium chloride, hexane, 80°C, 19 h; m-CPBA: m-chloroperoxybenzoic acid. B. Synthesis starting from thioanisole (V); VI: 4-(methylthio)acetophenone; VII: 4-(methylsulphonyl)acetophenone; VIII: 2-bromo-1-[4–(methylsulphonyl)acetophenone; MMPP: magnesium monoperoxyphthalate hexahydrate; Et_3N: triethylamine.

light and the presence of alkali. In their stability study conducted in two stress conditions (i.e., alkaline and photolytic), the group has established the degradation pathways leading to the formation of two major degradants (Figure 4). The first degradation reaction was the base-promoted hydrolysis of the γ-lactone moiety followed by its oxidation, yielding mainly a dicarboxylate derivative, with minor degradants being a hydroxyfuranone derivative and an anhydride derivative of rofecoxib (Figure 4B). The other degradation reaction is photo-

Table 1 Reported spectral characteristics for the identification of rofecoxib.

Study	Medium/solvent	Spectral characteristics
UV	Methanol	λ_{max}: 285 nm
IR	KBr	ν: 1745 cm^{-1}
^{1}H NMR	Acetone-d_6	δ = 7.96 (d, 2H, J = 8.4 Hz); = 7.68 (d, 2H, J = 8.4 Hz); = 7.42 (s, 5H); = 5.37 (s, 2H); = 3.15 (s, 3H)
^{1}C NMR	DMSO-d_6	δ = 172.4, 156.0, 142.0, 135.8, 129.8, 129.1, 128.9, 128.8, 128.7, 127.4, 126.9, 70.9, 43.1
MS (Pos ESI):	—	$[M+H]^+$: 315.1

(Thérien et al 2001; Reddy et al 2002).

cyclization of the cis-stilbene moiety resulting in the formation of a phenathrene derivative (Figure 4A). A similar photo-degradant has recently been reported by Hartman et al (2002) on subjecting the drug to photolytic stress. However, no significant degradation was observed in the separate oxidative stress conditions carried out in the presence of 6% hydrogen peroxide (Mao et al 2002).

Analytical methodologies

Determination of rofecoxib in biological fluids Various assay procedures reported for estimation of rofecoxib in biological fluids have been summarized in Table 2. Woolf et al (1999) developed a high-performance liquid chromatographic (HPLC) assay for the determination of rofecoxib in human plasma after oral administration. It employed the principle of liquid–liquid extraction for sample preparation followed by HPLC with post-column photochemical derivatization and fluorescence detection. In the post-column derivatization methodology, upon exposure to UV light, rofecoxib was found to undergo a stilbene phenanthrene-like photocyclization reaction with the formation of highly fluorescent species (Figure 4A). The method is reported to be highly sensitive, precise and accurate for the analysis of plasma samples in the drug concentration range of 0.5–100 ng mL^{-1} collected during clinical pharmacokinetic studies in man. Chavez-Eng et al (2000) have described another HPLC estimation procedure for rofecoxib in human plasma that employs atmospheric pressure chemical ionization tandem mass spectrometric (APCI-MS-MS) detection. The precision of the assay, expressed as coefficient of variation, has been documented to be less than 10% at all the concentrations within the range 0.1–100 ng mL^{-1}, with adequate assay accuracy. Jamali & Sattari (2000) reported a simple, rapid and sensitive method for estimation of rofecoxib in rat and human plasma using reversed-phase HPLC (RP-HPLC) with UV detection. Another analytical technique explained by Werner et al (2001) for the estimation of rofecoxib in human plasma involves the use of RP-HPLC coupled with APCI-MS-MS. The APCI-MS-MS is employed with Finnigan Mat LCQ ion trap spectrometer in contrast to the API III Plus triple quadrupole tandem mass spectrometer employed by Chavez-Eng et al (2000). Similar results were obtained at negative ion trap mode with both assays. However, at positive ion mode, Werner et al (2001) observed a different main daughter of rofecoxib in mass spectroscopy without endogenous interferences and thus claim their assay method to be more sensitive at positive ion mode than that described earlier by Chavez-Eng et al (2000).

Further, Matthews et al (2002) have reported HPLC determination of rofecoxib with improved extraction of the analyte and internal standard from human plasma. The solid-phase extraction employed for the purpose yielded an assay throughput 3-times better than that reported previously by Woolf et al (1999). A method employing HPLC coupled with APCI-MS-MS has recently been published for the simultaneous estimation of rofecoxib and its stable isotope analogue ([^{13}C7]rofecoxib) in human plasma (Chavez-Eng et al 2002). This simultaneous estimation is helpful in the quantification of rofecoxib in clinical bioavailability studies, where the oral dose of rofecoxib (12.5 mg or 25 mg) is co-administered with an intravenous dose of the isotope analogue. Another recent study (Aravind et al 2002) reports a rapid and sensitive HPLC estimation procedure for rofecoxib in human serum. The researchers report over four-week stability of the drug in serum and recommend their method to be suitable for estimation of the drug in samples collected from paediatric patients.

Determination of rofecoxib in bulk drug and pharmaceutical dosage forms Various analytical methods reported for rofecoxib in the bulk drug and pharmaceutical dosage forms are summarized in Table 3. Radhakrishna et al (2001) reported a method employing RP-HPLC method coupled with photodiode array detection for the estimation of rofecoxib in the bulk drug as well as the dosage forms. Krishna Reddy et al (2002) utilized this method along with mass spectrometery to establish two process-related impurities of rofecoxib in the bulk drug. These impurities were finally established as 4-[4-(methylsulphonyl)phenyl]-3-phenyl-5-hydroxyfuran-2-one and 4-[4-(methylsulphonyl)phenyl]-3-phenyl-2,5-furandione (Figure 5). Besides, two other HPLC assay methods have been reported by Ajithadas et al (2001) and Mao et al (2002). The latter have also reported the stability-indicating assay procedure for the isolation and identification of the two main degradants obtained under alkaline and photolytic stress conditions (Figure 4). Also, lately, the

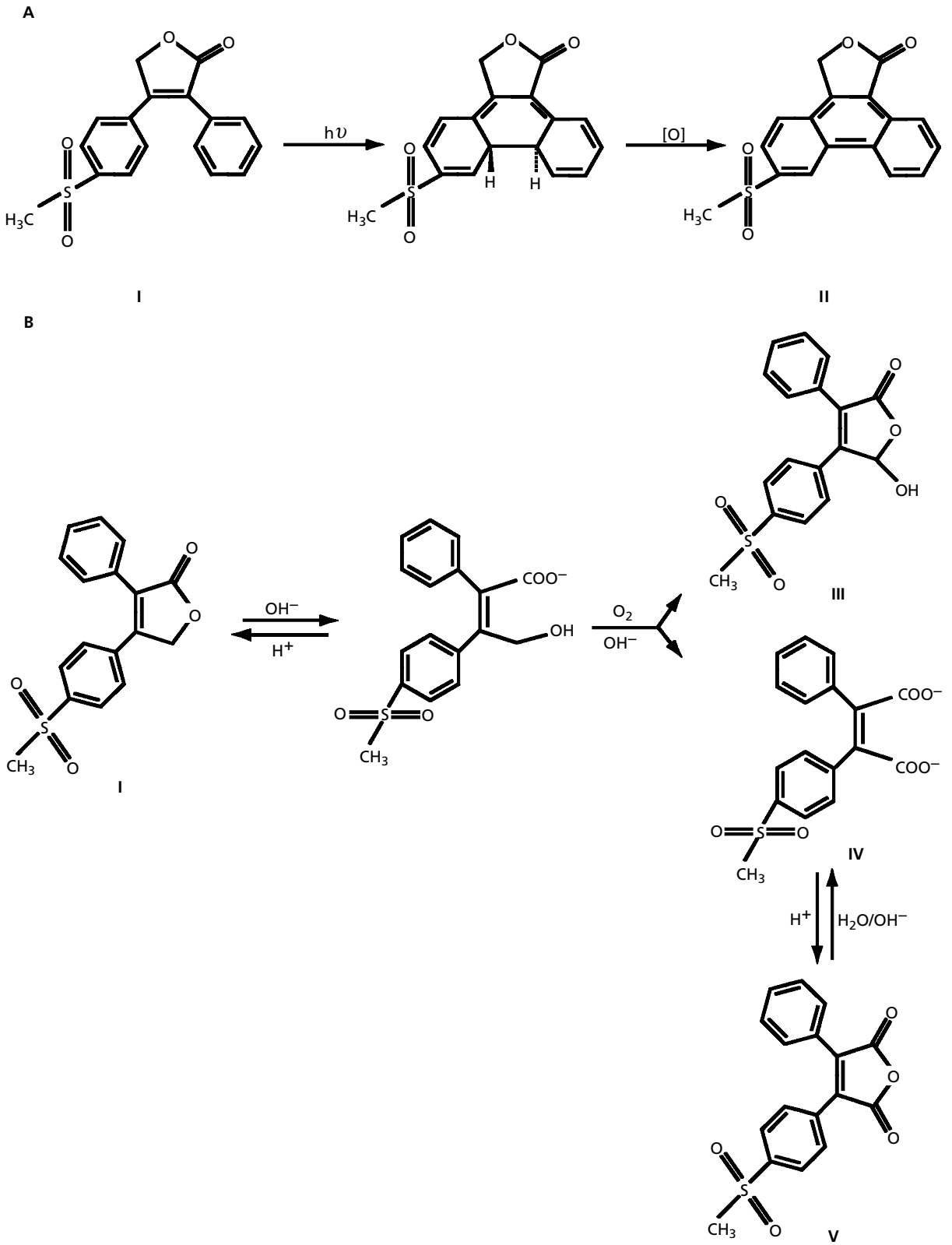


Figure 4 A. Degradation pathway of rofecoxib upon UV exposure. I: rofecoxib; II: 6-(methylsulphonyl)phenanthro[9,10-C]-furan-1(3H)-one. B. Degradation pathway of rofecoxib upon base catalysed hydrolysis III: 4-[4-(methylsulphonyl)phenyl]-3-phenyl-5-hydroxy-2-furanone; IV: 2-[4-(methylsulphonyl)phenyl]-1-phenyl-ethylene dicarboxylate; V: 4-[4-(methylsulphonyl)phenyl]-3-phenyl-2,5-furandione.

Table 2 Summary of various methods documented in literature for the analysis of rofecoxib in biological fluids.

Method	Extracting solvent	Internal standard	Mobile phase	LOQ (ng mL^{-1})	Biological fluid(s)	Reference
Solid phase extraction followed by HPLC with post column photochemical derivatization and fluorescence detection	Acetonitrile	Methyl derivative of rofecoxib	Acetonitrile–water (6.5:3.5 v/v)	0.5	Human plasma	Matthews et al (2002)
HPLC with APCI-MS-MS for simultaneous determination of the drug and its isotope analogue	Methyl-tert-butyl ether	Methyl derivative of rofecoxib	Acetonitrile–water (1:1 v/v)	0.1	Human plasma	Chavez-Eng et al (2002)
HPLC	—	—	—	20	Human serum	Aravind et al (2002)
RP-HPLC with APCI-MS-MS detection	Hexane–methylene chloride (1:1 v/v)	Celecoxib	Methanol–water (1:1 v/v) with 1% acetic acid	1.0	Human plasma	Werner et al. (2001)
HPLC with APCI-MS-MS detection	Hexane–methylene chloride (1:1 v/v)	Methyl derivative of rofecoxib	Acetonitrile–water (1:1 v/v)	0.1	Human plasma	Chavez-Eng et al (2000)
RP-HPLC with UV detection at 272 nm	Ethyl acetate	Ketoprofen	Acetonitrile–water (7.7:7.3 v/v) with 0.1% acetic acid and 0.03% triethylamine	10	Rat and human plasma	Jamali and Sattari (2000)
HPLC with post-column photochemical derivatization and fluorescence detection	Hexane–methylene chloride (1:1 v/v)	Methyl derivative of rofecoxib	Hexane–methylene chloride (1:1 v/v)	0.5	Human plasma	Woolf et al (1999)

LOQ: Limit of quantification; APCI-MS-MS: atmospheric pressure chemical ionization with tandem mass spectrometric detection; RP-HPLC: reversed-phase high-performance liquid chromatography.

Table 3 Summary of various methods documented in literature for the analysis of rofecoxib in bulk drugs and pharmaceutical dosage forms.

HPLC methods

Method	Extracting solvent	Internal standard	Mobile phase	LOQ ($\mu g\,mL^{-1}$)	Bulk drug/dosage forms	Reference
RP-HPLC with photo diode array detection	Acetonitrile–water (1:1) with 1M sodium hydroxide ($2\,\mu g\,mL^{-1}$)	—	Acetonitrile–phosphoric acid (3:7; 4:6; 8.5:1.5 v/v)	—	Determination of degradants of rofecoxib in bulk drug	Mao et al (2002)
RP-HPLC with photo diode array detection	Acetonitrile	Chlorophenyl methyl sulphone	Acetonitrile–water (1:1 v/v)	125	Bulk drug and pharmaceutical formulations	Radhakrishna et al (2001)
RP-HPLC with UV detection at 254 nm	Ethanol	—	Acetonitrile–water (1:1 v/v)	100	Pharmaceutical solid dosage forms	Ajithadas et al (2001)

Spectrophotometeric methods

Method	λmax	Molar extinction coefficient	Conc. range of linearity ($\mu g\,mL^{-1}$)	Bulk drug/dosage forms	Reference
UV in methanol medium	285 nm	2.8449×10^4	5–40	Pharmaceutical solid dosage forms	Reddy et al (2002)
UV-visible spectrometric detection of chromogen formed with ferric chloride and 3-methyl-2-benzothiazolinone hydrazone hydrochloride	625 nm	0.5721×10^4	5–40	Pharmaceutical solid dosage forms	Reddy et al (2002)

RP-HPLC: reversed-phase high-performance liquid chromatography; LOQ: minimum concentration obtained from the linear calibration curve.

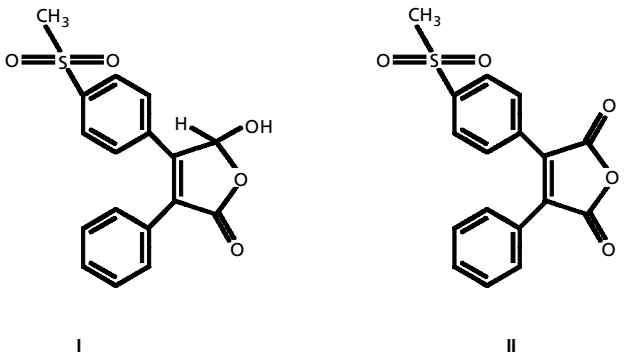


Figure 5 Chemical structures of the two process related impurities found in the rofecoxib bulk drug. I: 4-[4-(methylsulphonyl)phenyl]-3-phenyl-5-hydroxyfuran-2-one; II: 4-[4-(methylsulphonyl)phenyl]-3-phenyl-2,5-furandione.

determination of rofecoxib employing both UV and visible spectrophotometry has been described by Reddy et al (2002). Radi (2002) has reported the estimation of rofecoxib in pharmaceutical preparations without sample pretreatment. The author employed cyclic and square-wave voltammetery on a hanging mercury drop electrode in electrolytes of various pH values.

Pharmacodynamic aspects

Mechanism of action: COX-2 selectivity

The mechanism of action for the anti-inflammatory, analgesic and antipyretic activity of rofecoxib (Figure 6) is believed to be due to the inhibition of prostaglandin synthesis via inhibition of COX-2 (Merck & Co. 1998; Chan et al 1999). At therapeutic concentrations in man, rofecoxib is not known to inhibit the COX-1 isoenzyme.

Both COX-1 and COX-2 are associated with cell membrane, and consist of a long and narrow channel with a hairpin bend at one end and a hydrophobic opening at the other end (Picot et al 1994; Luong et al 1996; Hawkey 1999; Rehman & Sack 1999). Regular NSAIDs inhibit both the isoforms by hydrogen bonding, blocking the COX enzyme channel halfway down. The COX-2 isoform, however, has a side pocket guarded by valine at position 523, which is believed to be the site of binding of COX-2 specific inhibitors (blocked often by sulphonyl, sulphone or sulfonamide groups of COX inhibitors to achieve selectivity). COX-2 inhibition is time dependent and irreversible, in contrast to COX-1 inhibition, which is instantaneous and competitively reversible (Hawkey 1999).

The isoform selectivity of rofecoxib has been evaluated with diverse in-vitro enzyme and cell-based assay systems (Meade et al 1993; Mitchell et al 1994; Kargman et al 1996; Berg et al 1997; Miralpeix et al 1997; Wong et al 1997; Kirtikara et al 2001; Shen et al 2002). Rofecoxib has been found to be a potent inhibitor of COX-2 in a variety of cell-based assays (e.g., osteosarcoma cells, Chinese hamster ovary cells, lipopolysaccharide (LPS)-induced human mononuclear cells, sfa rat cells, etc.) with 50% inhibitory concentrations (IC50) varying between 0.018 and 0.0446 μM (Chan et al 1999; Ehrich et al 1999a). This value is markedly lower than the magnitude of IC50 for COX-1 ($>50\ \mu$M) (Chan et al 1999). Hence, it exhibits over 1000-fold selectivity for inhibition of COX-2 in comparison with COX-1. In contrast, the IC50 values reported for COX-1 and COX-2 inhibition with a non-selective NSAID, indometacin, were 0.018 and 0.027 μM, respectively (Ehrich et al 1999a). In recombinant enzyme assays, the IC50 value of rofecoxib for COX-2 was observed to be $1.8 \times 10^{-5}\ \mu$M as compared with $1.5 \times 10^{-2}\ \mu$M for COX-1, indicating once again nearly a 1000-fold selectivity towards COX-2 (Jackson & Hawkey 2000).

The in-vitro human whole blood COX-1 and COX-2 assays indicated that rofecoxib has the highest in-vitro selectivity ratio (COX-1 IC50/COX-2 IC50 = 35.5) among many of the commonly used NSAIDs such as celecoxib (6.6), meloxicam (2), diclofenac (3) and indometacin (0.4) (Chan et al 1999). However, recently, Kato et al (2001) observed the IC50 value of rofecoxib for COX-2 to be 25 μM and the selectivity index of rofecoxib as lower than that of various NSAIDs like celecoxib and meloxicam, employing human peripheral monocytes as a novel model to determine the COX-2 selectivity. Nevertheless, the validity of this model to document selectivity index needs to be investigated further.

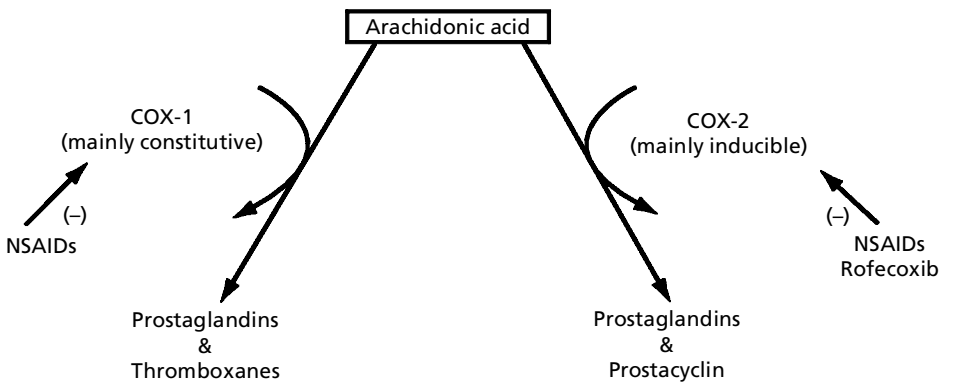


Figure 6 Mechanism of action of rofecoxib vis-â-vis nonselective NSAIDs.

The ex-vivo human whole blood assays showed the dose-related inhibition of COX-2 activity. The drug showed a COX-1 sparing effect, as it did not affect the platelet thromboxane production (a measure of COX-1 activity) at doses even up to 1 g daily (Chan et al 1999, Cannon et al 2000; Depré et al 2000). In man, the mean IC50 value for single doses of rofecoxib for LPS-stimulated prostaglandin E_2 (PGE_2) production (an indicator of COX-2 activity) in healthy subjects is reported to be 0.77 μM over a dose range of 25–1000 mg vis-à-vis the IC50 value for indometacin of 0.3 μM over the dose range of 5–75 mg. There was no significant inhibition of thromboxane B_2 (TxB_2) generation with rofecoxib at single doses of up to 1000 mg, whereas the IC50 value for indometacin was found to be 0.09 μM (Ehrich et al 1999a). Similar results have been observed by Wight et al (2001), who reported that rofecoxib (50 mg), when compared with placebo, inhibited LPS-stimulated PGE_2 significantly (79%, $P < 0.001$) with no significant effect on serum-generated TxB_2 ($P > 0.100$), while naproxen (500 mg) significantly inhibited both LPS-stimulated PGE_2 and serum-generated TxB_2 by 77% and 94%, respectively ($P \leq 0.002$ in each case). On multiple dosing, the IC50 value of rofecoxib was found to be 0.93 μM (Depré et al 2000), in consonance with the results obtained in the aforementioned single-dose study.

Different methods of quantifying COX-2 selectivity yield varying results and the lack of a common method leads to confusion about the relative COX-2 selectivity of the antiphlogistic agents (Loewen 2002). The results of in-vitro assays are useful for drug screening but are difficult to interpret and are sometimes contradictory (Cronstein 2002). This may be attributed to diverse factors like the nature of enzyme and substrate employed, incubation period and other experimental variables. Therefore, because of varying sensitivity to assay conditions, the quantitative comparisons between methods should be approached with caution. Whole-blood assays are far more relevant pharmacologically (Ehrich et al 1999a Cronstein 2002). These assays are performed in a physiologic medium (i.e., whole blood) with endogeneous enzymes and locally derived substrate(s). In-vitro whole-blood studies are performed by the addition of drug in various concentrations to blood previously obtained. Performance of ex-vivo whole-blood assays on blood samples collected after systemic drug administration represents further refinement in ascertaining the isoenzyme selectivity. These assays, therefore, are the most widely accepted methods for the determination of selectivity. The ex-vivo assays directly test the selectivity of both the parent drug and any potential metabolites generated in-vivo at therapeutic blood concentrations. However, there is skepticism about the selectivity seen in blood that may not reflect selectivity at the gastric mucosa.

Therapeutic efficacy: osteoarthritis

American College of Rheumatology (ACR) guidelines for the medical management of osteoarthritis (OA) recommend the use of analgesics such as paracetamol, COX-2 inhibitors or conventional NSAIDs, in combination with exercise, education and social support (Detora et al 2001; Schnitzer 2001). Therapeutic drug trials for OA of the knee or hip often involve a number of efficacy measures (primary end points) including both patient and investigator global assessment of disease status or activity, and response to therapy. Typically, the patient's self-assessment includes the measure of pain and stiffness in the affected joint(s), and physical function or disability (Bellamy 1995). Western Ontario and McMaster Universities Index (WOMAC) is a commonly used specific health status measure for OA (Bellamy et al 1988; Ehrich et al 2000). Patient's global assessment of disease status and pain upon walking are assessed using Visual Analogue Scale (VAS) (0 mm = very well/no pain to 100 mm = very poor/extreme pain) or Likert scale (ranging between 0 and 4) while patient global assessment of response to therapy (PGART) is assessed on the scale of 0 (none) to 4 (excellent). Similarly for the trials that included the investigator's assessment of disease status, the scale ranged between 0 (very poor) to 4 (very well) (Matheson & Figgitt 2001).

In the treatment of patients with OA, rofecoxib administration once daily has been compared with that of placebo (Ehrich et al 1999b, 2001), celecoxib (Geba et al 2002), paracetamol (Geba et al 2002), diclofenac (Cannon et al 2000), ibuprofen (Day et al 2000; Saag et al 2000), naproxen (Matheson & Figgitt 2001) and nabumetone (Truitt et al 2001) with the duration of trials ranging from 1 to 52 weeks. The majority of the studies were conducted on patients with OA of the knee or hip in a randomized, placebo-controlled and double-blind manner.

Rofecoxib 12.5–50 mg daily has been reported to be more effective than placebo in a 6-week double-blind study in patients with OA (n = 672) (Ehrich et al 2001). In another study (Ehrich et al 1999b), rofecoxib (25 and 125 mg daily), when compared with placebo in 262 patients with OA of knee following varied periods of treatment (i.e., one, two and six weeks), exhibited significant improvement in the primary end points, the WOMAC pain subscale and patients' assessment of arthritic pain ($P < 0.001$ for both dosages). In comparison with placebo, rofecoxib also proved to be efficacious for the secondary end points, WOMAC physical function (~46% vs 11% improvement from baseline) and stiffness subscales (47–50% vs 11%), and patient and investigator global assessment of disease status and response to therapy (46–57% vs 11–19%, $P < 0.001$). No significant difference was observed between the effects obtained following administration of the two dosages of rofecoxib for any end point.

In one report (Detora et al 2001), data obtained from three 6-week double-blind trials (n = 1501) have been analysed to find the efficacy of rofecoxib in subpopulations of patients with OA, identified by demographic or base disease characteristics, or varied OA involvement. Rofecoxib (12.5 or 25 mg) showed generally consistent efficacy across subgroups of patients identified by sex, race, age, OA location(s), prior OA therapy, baseline study, joint tender-

ness or swelling (patients with knee OA only) and American Rheumatism Association (ARA) functional class levels. Overall in this combined analysis, no specific factor predicted a differential treatment effect to rofecoxib. Rofecoxib has been reported to improve quality of life both in the physical and mental domain of the SF36 questionnaire over six weeks in OA patients, as compared with placebo (Hawkey 1999).

Based on the primary endpoints, various studies have shown rofecoxib (12.5 or 25 mg daily) to be as effective as ibuprofen 800 mg three times daily over six weeks ($n = 736$) (Saag et al 2000) or diclofenac 50 mg three times daily over 6–12 months ($n = 784$) (Cannon et al 2000). All three treatments were comparable in improving the aforementioned parameters in addition to stiffness, joint tenderness and functional subscales.

A further placebo-controlled study, carried out in patients with OA of the knee or hip ($n = 341$, age ≥ 80 years), compared rofecoxib (12.5 mg or 25 mg) and nabumetone (1500 mg) with placebo for a duration extending to six weeks (Truitt et al 2001). Mean changes from baseline in the patient global assessment of disease status, measured using VAS scale, were significantly greater with both rofecoxib ($\sim$25 mm for both dosages) and nabumetone (26 mm) than with placebo (15 mm) ($P < 0.001$).

Results from a one-week-long comparative trial of rofecoxib (12.5 mg once daily) and naproxen (500 mg twice daily) showed no difference between them in the improvement from baseline in pain upon walking (86% vs 85%, respectively) (Matheson & Figgitt 2001). However, the results must be interpreted with caution, as the one-week duration of this trial is not long enough to reflect an improvement in OA accurately.

In a prolonged one-year trial, comparison of the performance of rofecoxib (12.5 and 25 mg) with that of diclofenac (50 mg three times daily) in patients with OA of the knee and hip ($n = 784$) demonstrated clinically comparable efficacy, as assessed by all the three primary end points (Cannon et al 2000). Results from secondary end points were also consistent with those of primary endpoints. However, there were small statistical differences favouring diclofenac in two of the endpoints (patient's assessment of response to therapy and physician's assessment of disease status), but these differences and their respective 95% confidence intervals (CI) were well within the clinical comparability bounds predefined for this study.

Efficacy of rofecoxib (12.5 mg once daily) has been compared with Arthrotec (combination of misoprostol 200 μg and diclofenac 50 mg; twice daily) (Acevedo et al 2001). The results of this 6-week study showed no significant difference in efficacy on OA pain, as measured by PGART (-19.9 mm and -22.5 mm on VAS, $P = 0.241$) and investigator's global assessment of disease status (-0.94 and -0.91 on Likert scale, $P = 0.622$). Rofecoxib rather showed improved gastrointestinal tolerability as compared with Arthrotec.

In a different 6-week trial, rofecoxib (12.5 or 25 mg) was compared with placebo and ibuprofen (800 mg three times daily) in adult patients with OA of the knee and hip ($n = 809$) (Day et al 2000). Ibuprofen, as well as rofecoxib, exhibited significantly greater efficacy than placebo ($P < 0.001$ each). Both the doses of rofecoxib demonstrated clinically comparable efficacy with that of ibuprofen, as assessed by primary and secondary endpoints. These results, obtained in a large and diverse population of patients from 26 different countries, were found to be consistent across race, age, sex, study, joint and prior OA medication use (NSAID vs paracetamol). Data also showed that doses of 12.5 and 25 mg provided comparable clinical efficacy and eventually 12.5 mg of rofecoxib was recommended as the initial dose for the treatment of OA.

Rofecoxib 25 mg daily produced a better clinical response than paracetamol 1000 mg daily after day 2 in 379 patients ($P < 0.01$), as observed during a 6-week randomized, double-blind trial (Matheson & Figgitt 2001). Rofecoxib 12.5 mg was also found to be superior to paracetamol for relieving rest pain on days 4 to 5. Fewer rofecoxib recipients withdrew from the trial (7.4% and 8.5% for 12.5 and 25 mg, respectively) as compared with paracetamol recipients (18%).

Comparison of rofecoxib (12.5 mg daily) with another coxib (i.e., celecoxib 200 mg daily) indicated better performance of the former in relieving night pain on day 2 and 3 and rest pain on days 2–6 ($P < 0.05$) in 379 patients in a six-week randomized, double-blind trial (Matheson & Figgitt 2001). Rofecoxib was also significantly more effective than celecoxib in relieving pain while walking on days 2–4 ($P < 0.05$). In a recent trial (Geba et al 2002), rofecoxib (25 mg) has been found to be more efficacious than paracetamol (4000 mg daily), celecoxib (200 mg daily) and rofecoxib (12.5 mg).

In a nutshell, all the clinical findings reveal the efficacy of rofecoxib to be distinctly superior to that of placebo and either better than, or at least comparable with, the nonselective NSAIDs in treating patients with OA. The studies also suggest the initial dose of rofecoxib for the symptomatic relief of OA to be 12.5 mg once daily with a maximum dose of up to 25 mg once daily.

Therapeutic efficacy: acute pain

The NSAIDs are frequently used to relieve pain following minor surgery. Their administration from day one following major surgery reduces the requirement for opioids considerably, thereby decreasing the risk of sedation, respiratory depression and gastrointestinal complications (Reuben & Connelly 2000; Katz 2002). Rofecoxib has also been found to relieve moderate to severe pain in acute analgesic models of postoperative dental pain and postorthopaedic surgical pain (Merck & Co. 1998; Scott & Lamb 1999; Matheson & Figgitt 2001; Moore & Hersh 2001; Barden et al 2002).

Postsurgical dental pain

Rofecoxib has been evaluated for doses of 7.5–500 mg and has been compared with NSAIDs such as naproxen sodium, ibuprofen and celecoxib, and with placebo (Morrison et al 2000). Several studies have indicated the unambiguous superiority of rofecoxib as an analgesic to placebo (Mehlisch et al 1998;

Brown et al 1999a; Fricke et al 1999; Malmstrom et al 1999, 2002; Morrison et al 1999a). The analgesic efficacy has been assessed on the basis of the scores of parameters such as total pain relief over 8 h (TOPAR8), pain intensity difference (PID), summed PID over 6 or 8 h (SPID6/8), global evaluation of the study at 6 or 8 h, time to meaningful pain relief, time to PID ≥ 1, peak pain relief, peak PID during the first 6 or 8 h after dosing, etc.

The results of the various double-blind, parallel-group studies have also consistently demonstrated the efficacy of rofecoxib in postsurgical dental pain models. In a randomized, double-blind, placebo-controlled trial of rofecoxib (50 mg) conducted in dental patients (n = 151) for its effect in postoperative pain, rofecoxib provided an analgesic effect superior to placebo and equivalent to ibuprofen (400 mg), but with relatively longer duration of action ($P < 0.05$) (Brown et al 1999a; Morrison et al 1999a). The effect of rofecoxib as an analgesic was significant for all the endpoints like TOPAR8, SPID8, patient global evaluation, peak pain relief, peak PID, percent re-medicated within 24 h, time to re-medication ($P < 0.001$ for all) and stopwatch time to confirmed perceptible relief ($P < 0.007$). Similar results have been observed in a separate study (involving 102 patients), wherein the efficacy of rofecoxib (50 and 500 mg) was found to be superior to placebo and clinically indistinguishable with ibuprofen (400 mg) (Ehrich et al 1999b). The onset of pain relief with rofecoxib, as assessed by median time to meaningful pain relief, with both 50 mg (1.5 h) and 500 mg (1.2 h) was similar to that observed with ibuprofen (1.2 h) and significantly shorter ($P < 0.002$) than that with placebo (4.5 h).

In another comparative clinical study conducted in patients (n = 331), rofecoxib (25 and 50 mg) provided analgesic efficacy generally similar to naproxen sodium 550 mg (Fricke et al 1999). Rofecoxib was found to be superior to placebo (for all the primary and secondary end points) and doses of 25 and 50 mg were found to be significantly better than 12.5 mg ($P < 0.001$ for primary endpoint TOPAR8; $P \leq 0.006$ for secondary endpoints).

A dose–response relationship has been observed with rofecoxib in the treatment of postsurgical dental pain (Mehlisch et al 1998). A 50-mg dose of rofecoxib produces an analgesic effect comparable with that of 100 mg and with that of naproxen 550 mg. The study suggests that the 50-mg dose is the minimal dose necessary to yield maximal analgesic efficacy.

In the third molar post-extraction model, comparison of the analgesic efficacy of rofecoxib 50 mg with celecoxib 200 mg, ibuprofen 400 mg and placebo, revealed the maximal analgesic efficacy of rofecoxib to be superior to that of celecoxib and placebo but equivalent to that of ibuprofen (Malmstrom et al 1999). Lately, Malmstrom et al (2002) have reported an extension to the above study to include another dose of celecoxib (i.e., 400 mg). They found that rofecoxib 50 mg provided generally superior overall analgesic efficacy to celecoxib 400 mg, with longer duration of action. However, the effect was similar to 400 mg ibuprofen but with longer duration of analgesia. Further, with respect to the duration of effect, the results can be somewhat misleading, as ibuprofen and celecoxib require multiple daily doses (Moore & Hersh 2001; Olszynski et al 2002). In another third molar post-extraction model (Chang et al 2001), rofecoxib was found to have an analgesic efficacy greater than that of a combination of codeine 60 mg and paracetamol 600 mg ($P < 0.001$ for all measures of analgesic efficacy), with a lower incidence of nausea ($P < 0.001$) and other common adverse events ($P < 0.05$).

Very recently, the efficacy of rofecoxib (50 mg) has been compared with enteric-coated tablets of diclofenac sodium (50 mg) in a randomized, double-blind, placebo-controlled trial conducted in 305 patients with moderate to severe pain associated with oral surgery (Chang et al 2002). A single dose of rofecoxib 50 mg was found to yield greater overall analgesic efficacy over 24 h than that obtained with the three doses of enteric-coated diclofenac sodium 50 mg repeated every 8 h. On comparison with single doses of enteric-coated tablet of diclofenac sodium (50 mg), a single 50-mg dose of rofecoxib provided greater overall analgesic efficacy over 8 h, more rapid onset of analgesia and longer duration of effect.

Morrison et al (2000) compiled the results of various clinical trials conducted to assess and compare the analgesic efficacy of rofecoxib for postsurgical dental pain. They concluded that rofecoxib exhibits dose-dependent analgesic efficacy, with a 50-mg dose being consistently more effective than placebo for all the measures of analgesic efficacy. Further, it was the lowest dose that reproducibly exhibited an analgesic effect comparable with that of maximum single analgesic doses of most NSAIDs. Thus, based on the results obtained from various studies, Morrison et al (2000) have suggested that a 50-mg dose is an appropriate analgesic dose of rofecoxib for the treatment of acute dental pain. However, further studies are required to determine whether inhibition of COX-2 alone is sufficient for analgesic efficacy in other pain syndromes, with a specific COX-2 inhibitor like rofecoxib. Also, based on the magnitude of dose, the studies suggest that the analgesic activity of rofecoxib is relatively poorer in contrast to its anti-inflammatory activity.

Postoperative pain Generally, opioids are prescribed for the management of postoperative pain. Because of the risk of gastrointestinal toxicity associated with the traditional nonselective NSAIDs, rofecoxib is prescribed frequently for the purpose nowadays (Afflitto 2000; Brooks & Day 2000; Barden et al 2002). It has allowed considerable reduction in morphine consumption following various postoperative procedures like spinal fusion, abdominal hysterectomy, lumbar disc surgery, total knee arthroplasty, etc. (Reuben & Connelly 2000; Bekker et al 2002; Meyer 2002; Reuben et al 2002a, b), and the US FDA has also admitted rofecoxib for alleviating postoperative pain (Berti et al 2001). Though rofecoxib has been found to reduce the opioid consumption postoperatively, it does not seem to affect the opioidergic system (Sandrini et al 2002). In their study conducted on rat brain, the authors concluded that rofecoxib might exert its antinociceptive effect partly through the central sero-

tonergic system without affecting the opioidergic system (Sandrini et al 2002; Sinatra 2002).

Rofecoxib has been found to be superior to placebo in its analgesic efficacy in postoperative pain (Matheson & Figgitt 2001; Reicin et al 2001). Rofecoxib (50 mg), when given before surgery, provides better efficacy and longer duration of analgesia than when the drug is administered postsurgically, thus leading to less opioid use (Reuben & Connelly 2000; Bekker et al 2002; Reuben et al 2002a). Rofecoxib has been evaluated for its efficacy in various randomized, double blind, placebo-controlled trials in patients undergoing orthopaedic surgery (Reicin et al 2001; Bekker et al 2002; Reuben et al 2002a, b), tonsillectomy (Pickering et al 2002), radical prostatectomy (Huang et al 2001), abdominal hysterectomy and laparascopic gastric bleeding (Meyer 2002).

Rofecoxib (50 mg), when tested in patients with post-orthopaedic surgery pain ($n = 218$), was observed to be superior to placebo and similar to naproxen (550 mg) for all the measures of pain relief (Reicin et al 2001). When administered 1 h before anaesthetic induction, rofecoxib 50 mg was significantly more effective than either celecoxib 200 mg (also given 1 h before anaesthetic induction) or placebo in relieving postoperative pain in patients ($n = 60$) with decompressive lumbar laminectomy with spinal fusion (Reuben & Connelly 2000). Postoperative mean verbal analogue scale scores for rofecoxib recipients were significantly lower at 8, 12 and 16 h as compared with placebo recipients, and at 12 and 16 h as compared with celecoxib recipients. The total dose of supplemental morphine was also significantly less with rofecoxib than with either placebo or celecoxib (71 vs 117 and 107 mg, respectively, $P < 0.001$ each). In another study conducted in 61 patients scheduled for lumbar disc surgery, preoperative administration of rofecoxib (50 mg) was found to be effective in reducing the postoperative narcotic consumption (Bekker et al 2002). One isolated clinical study (Pickering et al 2002) has evaluated the effectiveness of a combination of rofecoxib ($0.625\ mg\ kg^{-1}$) with paracetamol ($20\ mg\ kg^{-1}$) for peri-operative analgesia in children (aged 3–15 years) undergoing (adeno)tonsillectomy. The combination was found to be as effective as paracetamol alone in altering the need for early analgesia (68% vs 72%), indicating no need to combine rofecoxib with the latter. Reuben et al (2002a, b) reported that pre-operative administration of rofecoxib (50 mg) in patients with arthroscopic meniscectomy, as well as with those undergoing total knee arthroplasty, provides a longer duration of postoperative analgesia, lower 24-h opioid use, and lower incidental pain scores, in comparison with the post-operative administration of rofecoxib (50 mg).

In contrast to all of the above findings, Huang et al (2001) have demonstrated that the preoperative administration of rofecoxib is ineffective in reducing the pain scores and need for analgesia in patients undergoing radical prostatectomy. However, Matheson & Figgitt (2001) have inferred, on the basis of preliminary results obtained from various studies, that the efficacy of rofecoxib in relieving postoperative pain appears to be related to the specific indication being treated.

Therapeutic efficacy: dysmenorrhoea

Rofecoxib can be used as a sole agent in alleviating the pain caused due to primary dysmenorrhoea (Morrison et al 1999b; Scott & Lamb 1999; Brooks & Day 2000; Matheson & Figgitt 2001). It has been compared with naproxen sodium (550 mg) in two comparative, randomized, double-blind, placebo-controlled, crossover trials (Brown et al 1999b; Daniels et al 1999). In both the trials, rofecoxib was administered as a 50-mg initial dose followed by a maintenance dose of 25 mg daily as needed, and naproxen sodium was administered as a 550-mg initial dose followed by 550 mg every 12 h as needed. In one trial, rofecoxib was also initially administered as 25-mg dose followed by a 25-mg maintenance dose (Daniels et al 1999; Morrison et al 1999b). The efficacy of rofecoxib was evaluated on the basis of TOPAR8 (the primary end point) in both the trials, while in one of the trials (Daniels et al 1999) pain intensity at 8 and 72 h and need for additional doses of either the study drug or rescue medication were the other end points. Rofecoxib (25 or 50 mg) and naproxen sodium (550 mg) were significantly better than placebo in providing total pain relief up to 8 h after the onset of moderate to severe pain ($P \leq 0.006$) (Brown et al 1999b; Daniels et al 1999; Morrison et al 1999b). In one trial conducted on 63 patients, taking all the primary and secondary endpoints like TOPAR8, SPID8, peak pain relief, peak PID, time to re-medication and ranking of study drugs across cycles, rofecoxib was found to be superior to placebo ($P < 0.004$ for all the end points except $P < 0.002$ for TOPAR8) (Brown et al 1999b). Overall, rofecoxib was significantly more effective than placebo ($P < 0.009$) and similar in efficacy to naproxen sodium in the evaluation of study drugs and re-medication. Similar findings were recorded in 127 patients with primary dysmenorrhoea, where mean TOPAR8 scores were similar for both the doses of rofecoxib and of naproxen sodium (17.4, 18 and 18.4, respectively) and all were significantly better than placebo (12.5, $P < 0.006$) (Daniels et al 1999; Morrison et al 1999b). Rofecoxib at an initial dose of 50 mg was similar in efficacy to naproxen sodium in the patient's overall evaluation of the study drug (mean 2.0 vs 1.9 for naproxen sodium). Time to PID from baseline was significantly less for naproxen sodium (1 h) than either rofecoxib or placebo (1.5 h, $P < 0.006$). A greater proportion of placebo recipients (45%) required rescue medication within 12 h of pain onset or took additional doses of study medication (24%), than with either rofecoxib (~27% for both doses) or naproxen sodium (~30%) ($P < 0.006$ each). As a consequence of these clinical studies, the scientists concluded that rofecoxib is distinctly effective in the treatment of primary dysmenorrhoea, and COX-2 derived prostanoids play a role in its pathophysiology.

Therapeutic efficacy: rheumatoid arthritis

The selective COX-2 inhibitors have emerged as an important option in the treatment of rheumatoid arthritis (RA) (Sundy 2001; Schnitzer & Hochberg 2002; Garner et al 2002). The US FDA has recently approved rofecoxib for

use in RA, although only limited reports are available on its efficacy. A phase II, double-masked, placebo-controlled trial assessed the efficacy of rofecoxib (5, 25 and 50 mg) in comparison with placebo in an 8-week study in 658 patients with RA (Schnitzer et al 1999). Significant clinical improvement was observed in patients taking rofecoxib 25 and 50 mg as compared with placebo. However, the 5-mg dose of rofecoxib did not differ significantly from placebo. Compared with placebo (32%), a significantly greater number of the patients taking the drug in a dose of 25 mg (43.9%, $P = 0.025$) and 50 mg (49.7%, $P = 0.001$) completed the treatment and achieved an American College of Rheumatology 20 response. Patients in the rofecoxib 25-mg and 50-mg groups showed significant improvement in the key individual efficacy measurements, including patient global assessment of pain, patient and investigator global assessment of disease activity and Stanford Health Assessment Questionnaire Disability Index ($P < 0.05$ vs placebo in all the cases). After 8 weeks, placebo and rofecoxib 5 mg recipients were reassigned to either rofecoxib (25 or 50 mg) or naproxen (500 mg twice daily) for an additional 44 weeks (Matheson & Figgitt 2001). Even after 1 year of treatment, the improvements in the 8-week end points were maintained. Global efficacy of rofecoxib was similar to that of naproxen and there were no differences between those patients who were reassigned and those continuously receiving the same treatment.

In a separate large trial (Vioxx Gastrointestinal Outcomes Research (VIGOR)) conducted in over 8000 patients with RA, the efficacy of rofecoxib (50 mg once daily) was observed to be equivalent to that of naproxen (500 mg twice daily) (Bombardier et al 2000). Even though this study was primarily designed to evaluate gastrointestinal tolerability of rofecoxib, the secondary efficacy end points were also evaluated. After a median follow-up of nine months, the two groups hardly differed from each other in regard to various end points like Global Disease Activity score (GDA) and Modified Health Assessment score (MHA). Regarding the GDA score, the least square difference between the two groups (rofecoxib and naproxen) from the baseline for patient's assessment was 0.00 (95% CI: −0.03 to 0.03), and for investigator's assessment was 0.01 (95% CI: −0.02 to 0.04). The difference between the scores of MHA from baseline was observed to be 0.01 (95% CI: −0.01 to 0.04). In addition, the rates of discontinuation of treatment owing to lack of efficacy were low in both the groups (6.3% in the rofecoxib group and 6.5% in the naproxen group). Collectively, the clinical findings demonstrate comparable anti-inflammatory efficacy of rofecoxib and nonselective NSAIDs in patients with RA.

Therapeutic efficacy: fever

Schwartz et al (1999) conducted antipyretic investigations in monkeys and man. In monkeys, pyrexia was induced by intravenous administration of LPS ($6\,\mu g\,mL^{-1}$). Oral administration of rofecoxib and diclofenac ($3\,mg\,kg^{-1}$) both rapidly reversed the elevated temperature in the monkeys at 70–90 min postdosing in a significant manner ($P < 0.05$ each). In man, the single-dose, parallel group, double blind randomized trial conducted in 94 patients with fever caused by viral-type illness, rofecoxib (12.5 mg or 25 mg) was found to be superior to placebo ($P < 0.001$) and equivalent to ibuprofen (400 mg). The data support the hypothesis that it is the COX-2 isoform that is primarily involved in the genesis of fever in man. In another study conducted by Chan et al (1999) in rats, administration of rofecoxib reversed LPS-induced pyrexia in a dose-dependent manner ($ID50 = 0.24 \pm 0.07\,mg\,kg^{-1}$), being about five times more potent than indometacin ($ID50 = 1.07 \pm 0.16\,mg\,kg^{-1}$).

Accordingly, it can be construed that rofecoxib possesses antipyretic activity both in animals and man and its efficacy is comparable with that of nonselective NSAIDs like diclofenac, ibuprofen, etc.

Pharmacokinetic aspects

The pharmacokinetic fate of rofecoxib following its administration in single and multiple doses has been thoroughly evaluated in healthy subjects by several workers (Merck & Co. 1998; Depré et al 2000; Werner et al 2001; Halpin et al 2002). By and large, the pharmacokinetics of the drug has been found to be variable and complex. Various pharmacokinetic parameters of rofecoxib vis-à-vis of other important coxibs, as reported in literature, have been summarized in Table 4.

Absorption

Rofecoxib is almost completely absorbed after oral administration. The mean oral bioavailability after a therapeutically recommended single dose of rofecoxib (12.5, 25 or 50 mg) is 93% (Merck & Co. 1998). The area under the curve (AUC) and peak plasma level (C_{max}) following a single dose of 25 mg were observed to be 3286 ($\pm$843) ng h mL^{-1} and 207 ($\pm$111) ng mL^{-1}, respectively. Werner et al (2001) have lately reported various pharmacokinetic parameters in man following a 12.5 mg dose of rofecoxib. The values of AUC and C_{max} were found to be 2038 ($\pm$581) ng h mL^{-1} and 147 ($\pm$34) ng mL^{-1}, respectively. With multiple dosing, the steady state is reached by day 4 (Merck & Co. 1998). The values of AUC and C_{max} after multiple dosing (25 mg) have been observed to be 4018 ($\pm$1140) ng h mL^{-1} and 321 ($\pm$104) ng mL^{-1}, respectively. Both AUC and C_{max} increase in a dose-proportional manner up to 50 mg distinctly indicating linear pharmacokinetics across the clinical dose range of 12.5–50 mg. Further, Depré et al (2000) reported the dose-proportionality both after single and multiple doses even up to 100 mg. However, according to the authors (Merck & Co. 1998; Depré et al 2000; Halpin et al 2002), the lack of dose-proportionality in pharmacokinetic response at higher doses can be attributed to the low solubility of the drug in the aqueous media. The time taken to reach C_{max} (t_{max}) is 2–3 h, with individual values varying between 2 and 9 h (Merck & Co. 1998; Werner et al 2001). However, t_{max} may not reflect the true rate of absorption, as it may be obtained from secondary peaks in some individuals (Merck & Co. 1998). Halpin et al (2002)

Table 4 Pharmacokinetic parameters of rofecoxib vis-à-vis other commonly available coxibs following oral administration.

Pharmacokinetic parameter	Rofecoxib		Celecoxib 200 mg single dose	Valdecoxib 10 mg steady state	Etoricoxib 100 mg oral solution
	12.5 mg single dose	25 mg at steady state			
C_{max} (ng mL^{-1})	147 (± 34)	321 (± 104)	705 (± 267.9)	161.1 (± 48.1)	1362 (± 333)
AUC (ng h mL^{-1})	2038 (± 581)	4018 (± 1104)	—	1479 (± 291.9)	24400 (± 880)
t_{max} (h)	2.4 (± 1.0)	2–3	2.8 (± 1.03)	2.25 (± 0.71)	1.0 (± 0.5)
$t_{\frac{1}{2}}$ (h)	11.3 (± 2.1)	17	11.2 (± 3.47)	8.11 (± 1.32)	24.9 (± 6.0)
Vd (L)	91	86	429 (± 145.9)	—	—
CL (mL min^{-1})	141	120	461.7	—	108 (± 26)

(Merck & Co. 1998; Searle & Co. 1999; Depré et al 2000; Werner et al 2001; Halpin et al 2002; Searle Ltd. 2002; Rodrigues et al 2003).

reported the t_{max} to be 9 h postdose. They observed two secondary peaks for C_{max} between 0 and 6 h, and 20 and 26 h, respectively. Although the cause of secondary peaks with rofecoxib, mostly occurring at higher doses, is unknown, it has been suggested that it is not the result of enterohepatic recycling (Depré et al 2000). However, Halpin et al (2002) have concluded that, at higher doses, absorption is incomplete ostensibly due to its poor aqueous solubility. Since the absorption is slow and dependent upon intestinal motility, it results in the appearance of secondary peaks causing large variability in the t_{max}. Plasma concentration–time curves broaden with increasing doses (Depré et al 2000). The accumulation factor based on geometric means has been reported to be 1.67 (Merck & Co. 1998), whereas Depré et al (2000) observed an accumulation ratio of approximately 2 for all doses with a half-life ($t_{\frac{1}{2}}$) of around 20 h. Food appears to have no significant effect on either the C_{max} or AUC of rofecoxib when the drug is taken with a high-fat meal (Merck & Co. 1998), while the t_{max} can be delayed by 1–2 h. Thus, it can be deciphered that co-administration of food may affect the rate of absorption of rofecoxib but not the extent of oral absorption. Relative to man, oral absorption of rofecoxib ($5\,mg\,kg^{-1}$) is more rapid in animals, with the C_{max} occurring by 0.5 h in rats and 1.5 h in dogs (Halpin et al 2000).

Disposition

Rofecoxib is approximately 87% bound to plasma proteins over the drug concentration range of 0.05–$25\,\mu g\,mL^{-1}$ (Merck & Co. 1998). Not much is known about the distribution of rofecoxib into various human tissues. The value of the apparent volume of distribution at steady state (Vd_{ss}) is reported to be 91 L following a 12.5-mg dose and 86 L following a 25-mg dose. In dogs, its plasma clearance and Vd_{ss} has been reported to be $3.6\,mL\,min^{-1}\,kg^{-1}$ and $1.0\,L\,kg^{-1}$, respectively following intravenous administration of ^{14}C-rofecoxib ($5\,mg\,kg^{-1}$) (Halpin et al 2000). The drug has been found to be distributed rapidly to rat tissues, with a high proportion of the intravenous dose observed in most tissues by 5 min, and in liver, skin, fat, prostate and bladder by 30 min, as determined by radioactivity studies. No information is yet available on the possibility of rofecoxib crossing the placental or blood–brain barrier in man. However, it can cross the placenta in rats and rabbits, and the blood–brain barrier in rats (Halpin et al 2000).

Rofecoxib is metabolized primarily by cytosolic reductases with a minor role played by microsomal cytochrome P450 (CYP) (Merck & Co. 1998; Halpin et al 2002). Major metabolites (56%) in man have been identified to be cis-hydro and trans-hydro derivatives and minor metabolites (8.8%) as rofecoxib-3′,4′-trans-dihydrodiol, 4′-hydroxyrofecoxib-O-β-glucuronide, diastereomeric 5-hydroxyrofecoxib-O-β-glucuronide conjugates and 5-hydroxyrofecoxib (Figure 7). All the metabolites are inactive as COX-2 inhibitors. Biotransformation of rofecoxib and its glucuronide metabolite is reported to be reversible in man to a limited extent. Baillie et al (2001) have also reported similar results in rats. They observed two peaks for the C_{max} of rofecoxib in intact rats on administration of [4-^{14}C] rofecoxib at 1 h and later at 10 h. On administration of [4-^{14}C] 5-hydroxyrofecoxib to intact or bile-cannulated rats, two peaks for the C_{max} of rofecoxib were observed only in intact rats and not in bile-cannulated rats, suggesting the occurrence of reversible metabolism of rofecoxib to 5-hydroxyrofecoxib in the rat, which is dependent upon uninterrupted bile flow. However in contrast to man, this reversible metabolism is quite distinct in rats where 5-hydroxyrofecoxib is the major metabolite. Besides 5-hydroxyrofecoxib and its glucuronide derivative, other metabolites reported in rats include rofecoxib-3′,4′-dihydrodiol and 4′-hydroxyrofecoxib sulfate. Principal metabolites reported in dogs include, 5-hydroxy-O-β-glucuronide, and trans-3′4′ dihydro derivatives in urine, and 5-hydroxyrofecoxib in bile (Halpin et al 2000).

Rofecoxib is eliminated predominantly by hepatic metabolism with little (< 1%) unchanged drug recovered in urine (Merck & Co. 1998; Halpin et al 2002). Following a single radiolabelled dose of 125 mg, around 72% of the dose is excreted in the urine as metabolites and 14% in the faeces as unchanged drug.

As indicated in Table 4, higher plasma clearance at lower doses suggests the presence of saturable mode of metabolism (i.e., nonlinear elimination). The effective $t_{\frac{1}{2}}$ in steady state has been reported to be 17 h, while a range of 9.9–17.5 h has been observed after multiple dosing. However, a somewhat smaller value of $t_{\frac{1}{2}}$ (9.0 ± 2.7 h) has been reported by Werner et al (2001). In dogs, Halpin et al (2000) have reported the elimination $t_{\frac{1}{2}}$ of rofecoxib to be 2.6 h after intravenous administration of [^{14}C] rofecoxib.

Clinical pharmacokinetics

No report appears in literature indicating any effect of race or gender on the pharmacokinetics of rofecoxib. Nevertheless, a 34% increase in AUC was observed in elderly patients (age > 65 years), as compared with young subjects following single-oral-dose administration of 25 mg (Merck & Co. 1998). Though the manufacturer has not reported any dosage adjustment in geriatric patients, it has been recommended that therapy in these patients should be initiated with the lowest dose.

Hepatic insufficiency No significant difference in the values of AUC has been found between healthy subjects and patients with mild hepatic insufficiency with Child Pugh score $\leq$ 6 (Merck & Co. 1998; Schwartz et al 2000a). However, about 69% increase in AUC has been observed in patients with moderate hepatic impairment (Child Pugh score 7–9). Therefore, rofecoxib should be administered with caution to patients with moderate hepatic insufficiency. However, no data are available for patients with severe hepatic impairment.

Renal insufficiency The values of C_{max} and AUC have been reported to decline by 18 and 9%, respectively, in patients with end-stage renal failure undergoing dialysis

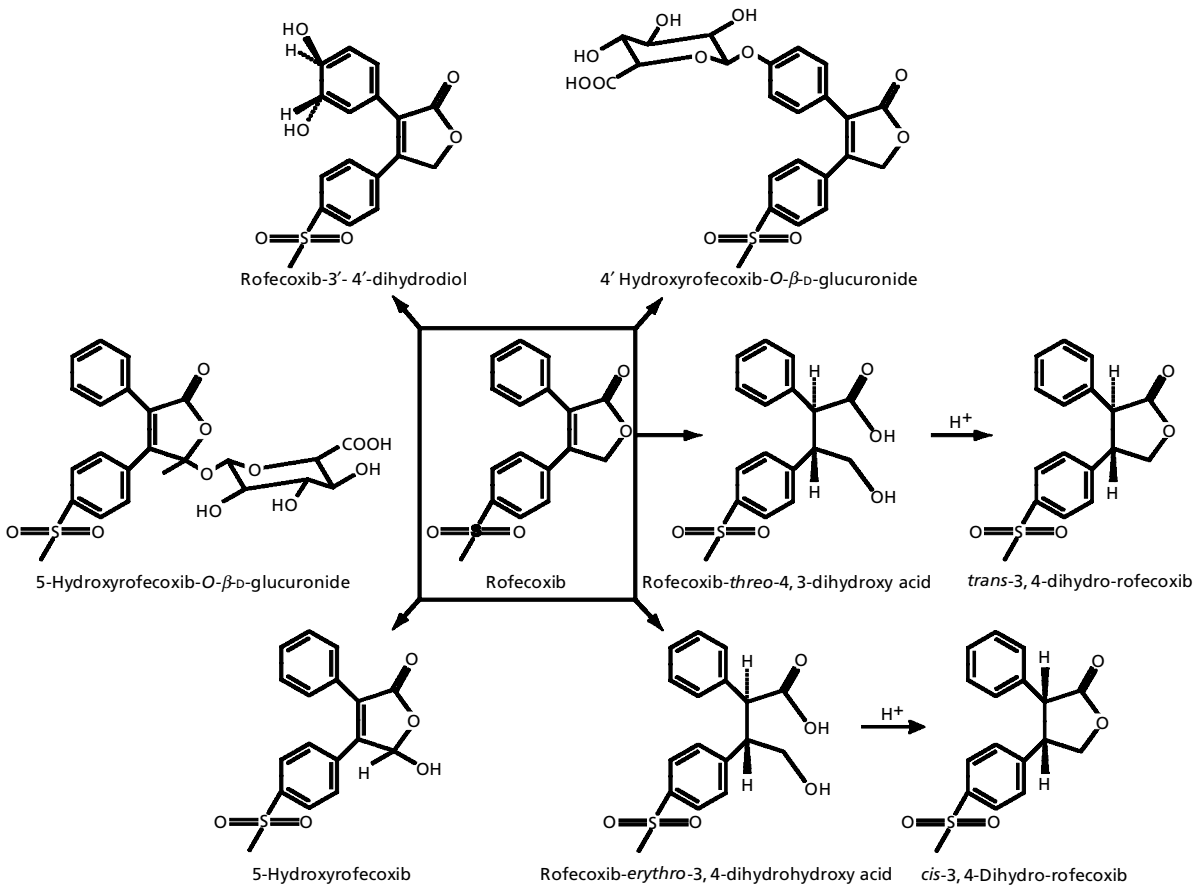


Figure 7 Pathways for biotransformation of rofecoxib to various metabolites in man.

(Merck & Co. 1998). Although the pharmacokinetics of rofecoxib has not been found to be influenced by renal impairment, its use has not been recommended in patients with renal failure (Brater et al 2001).

Drug interactions

Since NSAIDs are often prescribed to patients who have already been taking other drugs, the likelihood of occurrence of potential drug interactions increases manifold (Brouwers & de Smet 1994; Buchan & Bird 1991). However, rofecoxib being a relatively recent introduction, only moderate information is available on the reported interactions with this drug. Various reported drug interactions of rofecoxib, with pharmacokinetic or pharmacodynamic outcomes, have been compiled and are shown in Table 5.

Pharmacokinetic interactions

Rofecoxib is less likely to interact with other drugs as it is not extensively metabolized by CYP 450 enzymes (Merck & Co. 1998; Garnett 2001). Ketoconazole 400 mg administered concomitantly with rofecoxib 25 mg (n = 7) did not affect the blood levels of rofecoxib, whereas a 21% increase in the maximum plasma concentration of rofecoxib has been reported with cimetidine (800 mg twice daily), an inhibitor of CYP2D6, but no dosage adjustment has been recommended. On the other hand, co-administration of potent inducers of the CYP enzyme system, such as rifampin, carbamazepine, phenobarbital and phenytoin, may decrease the serum levels of rofecoxib. Rifampin 600 mg daily causes nearly a 50% decrease in plasma concentration of rofecoxib due to induction of general hepatic metabolic activity. Thus it has been advised by the author that when given along with a potent inducer, the patients should be prescribed a dose of rofecoxib higher than the normal one (Garnett 2001).

The effect of rofecoxib on CYP3A in man has been assessed by the intravenous erythromycin breath test (EBT) and oral midazolam test (Merck & Co. 1998; Garnett 2001; Matheson & Figgitt 2001). Rofecoxib (75 mg daily), when compared with placebo, produced no significant difference (P = 0.129) in erythromycin metabolism (Slaughter & Edwards 1995; Garnett 2001). On the contrary, rofecoxib (25 mg) produced a 30% decrease in 2 mg midazolam AUC (Merck & Co. 1998). This indicates the probability of moderate induction of intestinal CYP3A by rofecoxib and not of hepatic CYP3A. However, administration of rofecoxib, even in the diverse dosages of 25, 100, 250 and 375 mg, had no effect on the CYP3A-mediated metabolism of cortisol (Depré et al 2000). Rofecoxib 12.5, 25 and 50 mg has been found to increase

Table 5 Drug interactions of rofecoxib with various drugs.

	Interaction	Effect	Dosage adjustment recommendation
Effect of drugs on rofecoxib			
Ketoconazole	(−)	(−)	(−)
Cimetidine	(+)	AUC ↑ by 21%	(−)
Rifampin	(++)	AUC ↓ by 50%	Yes
Antacids (aluminium magnesium hydroxide, calcium carbonate)	(+)	C_{max} ↓ by 20%	(−)
Effect of rofecoxib on drugs			
Erythromycin	(−)	(−)	(−)
Midazolam	(+)	AUC ↓ by 30%	(−)
Cortisol	(−)	(−)	(−)
Theophylline	(++)	AUC ↑	(−)
Prednisolone & prednisone	(−)	(−)	(−)
Methotrexate			
with 25 mg rofecoxib	(−)	(−)	Standard monitoring for methotrexate
with 75 mg rofecoxib	(−)	AUC ↑ by 23%	toxicity recommended
Lithium	(+)	Renal clerance may ↑	Monitoring for lithium toxicity recommended
Aspirin	(−)	(−)	(−)
Warfarin	(+)	↑ in INR by 8%	Monitoring of INR recommended
ACE inhibitors (benzapril, lisinopril)	(+)	↑ in mean arterial pressure & alteration in antihypertensive effect	Yes
Diuretics (furosemide (frusemide), hydrochlorothiazide)	(+)	Blockade of drug induced aldosterone and renin activity	(−)

(−): no interaction or no dosage adjustment required; (+): mild interaction; (++): moderate interaction; AUC: area under the curve; C_{max}: peak plasma concentration; INR: international normalized ratio. (Schwartz et al 1997; Merck & Co 1998; Brown 2000; Schwartz et al 2000a; Garnett 2001; Kammerl et al 2001a, b; Matheson & Figgit 2001; Schwartz et al 2001a, b; Ho & Brighton 2002; Lundmark et al 2002; Schwartz et al 2002, 2003).

the theophylline AUC by around 40, 50 and 60% , respectively (Garnett 2001). As the metabolism of theophylline is mediated by CYP1A2, the above potentiation suggests the moderate inhibition of the enzyme by rofecoxib.

Rofecoxib at a dosage of 250 mg once daily for 14 days did not significantly alter the AUC of prednisone and prednisolone (30 mg oral and 35 mg i.v., respectively) in 12 healthy subjects ($P > 0.2$ for all treatment comparisons) (Merck & Co. 1998; Garnett 2001; Matheson & Figgitt 2001; Schwartz et al 2003). In patients with RA ($n = 21$), addition of rofecoxib in doses of 12.5, 25 and 50 mg daily to a stable methotrexate regimen (7.5–25 mg per week) had clinically no significant effect on the plasma concentration of the latter (Schwartz et al 2001a). However, a daily dose of 75 mg rofecoxib given concurrently with methotrexate (7.5–15 mg per week) for 10 days is known to enhance the AUC of this drug by 23% (Merck & Co. 1998). Consequently, standard monitoring (complete blood counts with differential and platelet counts, hepatic enzymes, renal function tests, etc., every 4–8 weeks) for methotrexate-related toxicity has been recommended when it is given along with rofecoxib. Further, the serum concentrations of ethinylestradiol or norethindrone in 18 healthy women were not significantly affected by the daily administration of rofecoxib at doses as high as 175 mg (Schwartz et al 1997, 2002). Also, the serum concentrations and urinary excretion of a single dose of digoxin (0.5 mg) were unaffected by once daily administration of 75 mg of rofecoxib for 11 days in 10 healthy subjects (Schwartz et al 2001b).

Co-administration of antacids (aluminium magnesium hydroxide suspension, 20 mL, or calcium carbonate suspension, 10 mL, with acid-neutralizing capacity of 50 mEq) with rofecoxib (25 mg) in healthy subjects ($n = 12$) did not produce any significant difference in plasma AUC, half-life or t_{max} (Merck & Co. 1998). However, C_{max} was reduced by 20% with both the antacids, indicating that the latter may prolong the rate of absorption of rofecoxib. Nevertheless, this interaction is unlikely to be of clinical importance.

Similar to NSAIDs, rofecoxib may decrease the renal clearance of lithium and thus may enhance lithium blood levels. As a consequence, when rofecoxib and lithium are administered concurrently, subjects should be observed carefully for any signs of lithium toxicity (Merck & Co. 1998; Garnett et al 2001; Lundmark et al 2002).

Pharmacodynamic interactions

Rofecoxib (50 mg) administered for 7 days to healthy subjects (n = 24) produced no effect on aspirin (81 mg)-induced inhibition of TxB_2 or platelet aggregation (Depré et al 2000; Greenberg et al 2000; Catella-Lawson et al 2001; Ouellet et al 2001). In subjects stabilized with daily warfarin (n = 15), addition of rofecoxib (25 mg daily) for 21 days led to an 8% mean increase in the international normalized ratio (INR). Therefore, monitoring of INR has been suggested for the first few weeks, when rofecoxib is given concomitantly with warfarin (Schwartz et al 2000b; Ho & Brighton 2002).

Patients who received rofecoxib (25 mg daily) and benazepril (10–40 mg daily) for 4 weeks had an average increase in mean arterial pressure of around 3 mmHg, as compared with patients receiving benazepril alone (Merck & Co. 1998). In another study, concomitant administration of rofecoxib (25 mg daily) with lisinopril resulted in impairment of the antihypertensive effect of the latter (10 mg daily) (Brown 2000). Therefore, when such drugs are given simultaneously with rofecoxib, blood pressure should be monitored regularly and their dosage should be adjusted accordingly.

Rofecoxib has been reported to completely block the aldosterone or renin activity induced by furosemide (frusemide) (Kammerl et al 2001a, b) or hydrochlorothiazide (Kammerl et al 2001b) in subjects on a salt-restricted diet and, consequently, it nullifies the salt-wasting effect of these diuretics. This interaction suggests that rofecoxib can be used in water and electrolyte wasting pathological conditions like Bartter and Gitelman diseases (Kammerl et al 2001b).

Tolerability: gastrointestinal effects

NSAIDs frequently produce untoward reactions particularly in the gastrointestinal tract (Singh et al 1996; Naesdal & Wilson 2001). During their short-term use, they cause extensive gastroduodenal erosions. During long-term use, around 15% of patients taking NSAIDs develop dyspepsia and about 2% develop serious ulcer complications, such as perforation, bleeding or gastric-outlet obstruction (Singh et al 1996). COX-2 inhibitors were developed in an effort to circumvent the gastroduodenal toxicity associated with non-selective NSAIDs (Scott & Lamb 1999). Endoscopic studies have shown that rofecoxib (25 and 50 mg once daily) exhibits an incidence of gastroduodenal ulcers equivalent to that found with placebo and significantly lower ($P < 0.001$) than with a comparator non-selective NSAID (ibuprofen 800 mg three times daily) (Laine et al 1999; Hawkey et al 2000).

Langman et al (1999) performed a meta-analysis of phase IIb/III trials of rofecoxib in patients with OA and observed a noticeable 49% reduction in the incidence of symptomatic gastrointestinal ulcers in patients taking rofecoxib at a median dose of 25 mg daily when compared with the non-selective NSAIDs, ibuprofen and diclofenac. Similarly, in the analysis of ulcer complication rates from 8 trials in patients with OA, rofecoxib over the dose range of 12.5–50 mg showed no more upper gastrointestinal perforation, ulcers or bleeding than placebo and considerably less than other commonly used non-selective NSAIDs (ibuprofen, diclofenac or nabumetone) (Watson et al 2000). The cumulative incidence of discontinuation due to gastrointestinal adverse effects during 12 months was significantly lower ($P = 0.02$) with rofecoxib than with NSAIDs (rates per 100 patient-years were 8.20 vs 12.03 for rofecoxib and NSAIDs, respectively). The cumulative incidence of pre-specified dyspeptic type gastrointestinal adverse effects during the first 6 months was significantly lower ($P = 0.02$) with rofecoxib (69.3 per 100 patient-years) versus NSAIDs (85.2 per 100 patient-years). However, the incidence rates converged after 6 months. VIGOR assessed the safety of rofecoxib with regard to gastrointestinal events in over 8000 patients with RA (age > 50 years) (Bombardier et al 2000). Treatment with rofecoxib (50 mg once daily) was found to be associated with significantly fewer clinically important upper gastrointestinal events than naproxen (500 mg twice daily). During a median follow up of 9 months, a score of 2.1 gastrointestinal events per 100 patient-years was observed with rofecoxib, as compared with 4.5 per 100 patient-years with naproxen (relative risk: 0.5; 95% CI: 0.3–0.6; $P < 0.001$). The respective rates of complicated confirmed events (perforation, obstruction and severe upper gastrointestinal bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years (relative risk: 0.4; 95% CI: 0.2–0.8; $P = 0.005$) for rofecoxib and naproxen, respectively. These clinical findings are encouraging as 50 mg rofecoxib is twice the maximum dose recommended for use in patients with OA. This lack of toxicity is further corroborated by a short-term (7-day) study in healthy subjects in which an even higher dose of rofecoxib (250 mg daily) was associated with a similar incidence of gastroduodenal injury to placebo and less than that observed with ibuprofen 800 mg three times daily or aspirin 650 mg four times daily (Lanza et al 1999).

A one-year study conducted in 784 patients demonstrated that fewer rofecoxib recipients experienced symptomatic ulcers (0.8%) than did diclofenac recipients (1.2%) (Cannon et al 2000). According to the authors, however, the number of patients in the study was relatively small to support the conclusion of a decrease in the incidence of perforation, ulcer and bleeding (PUB) events. Nonetheless, after pooling the data of all OA clinical studies, a statistically important decrease in PUB events was discerned for rofecoxib-treated patients (Langman et al 1999).

A double-blind, four-period crossover study in healthy subjects showed that intestinal permeability (as assessed by five-hour ^{51}Cr-EDTA/L-rhamnose urinary excretion ratio) after 7 days of treatment with rofecoxib (25 or 50 mg daily) was not significantly different from that observed with placebo (Sigthorsson et al 2000). In contrast, treatment with indometacin 50 mg three times daily increased intestinal permeability, as compared with both placebo and rofecoxib (25 mg and 50 mg daily) ($P < 0.001$). Mean ratios of ^{51}Cr-EDTA/L-rhamnose levels

at day 7 to baseline were 0.97 (95% CI: 0.82, 1.16), 0.80 (95% CI: 0.68, 0.95), 0.98 (95% CI: 0.82, 1.17) and 1.53 (95% CI: 1.27, 1.85) for placebo, rofecoxib 25 mg, 50 mg and indometacin groups, respectively.

The lack of effect of rofecoxib on intestinal permeability is consistent with the findings of a double-blind study in healthy subjects, which demonstrated that gastrointestinal microbleeding (measured using ^{51}Cr-labelled red blood cells in faecal matter) during rofecoxib therapy (25, 50 mg daily) was statistically significantly less than in the subjects treated with ibuprofen (2400 mg daily) ($P < 0.001$) (Hunt et al 2000). The gastrointestinal microbleeding with both doses of rofecoxib was observed to be equivalent to that seen with placebo.

In animal models, rofecoxib administered to rats at a dose of 300 mg kg^{-1} daily for 2 weeks did not produce any gastric or intestinal lesions (Chan et al 1999). This was further echoed by the gastrointestinal integrity observed during a study conducted using ^{51}Cr-labelled red blood cells as permeability markers. Rofecoxib had no effect even at a dose of 200 mg kg^{-1} daily for 5 days, whereas a 2- to 3-fold increase in faecal ^{51}Cr excretion was observed with indometacin at a single dose of 3 mg kg^{-1}. Also, they observed similar gastrointestinal sparing effect with rofecoxib (100 mg kg^{-1} twice daily for 5 days) in squirrel monkeys. Another study (Laudanno et al 2001) was carried out in Wistar rats to investigate the gastrointestinal effect of rofecoxib on normal healthy gastric mucosa and on gastric mucosa altered by indometacin-induced lesions. Rofecoxib did not exhibit any gastrotoxicity macroscopically as well as histologically in the healthy mucosa. In contrast, the lesions were aggravated in the altered mucosa (90%, $P < 0.001$) and most rats died on the third or fourth days. The experimental models involving gastric ulcers induced with acetic acid and duodenal ulcers with cysteamine further confirmed the aggravation of previously induced lesions. This suggested the role of COX-2 and its prostaglandins in the angiogenesis and healing of ulcers (Mizuno et al 1997; Laudanno et al 2001). This was further ratified by a recent study conducted by Guo et al (2002), where they observed that rofecoxib treatment (10 mg kg^{-1} daily) for 14 days in rats with gastric ulcers induced by acetic acid was associated with considerable increase in the ulcer size at 6, 10 and 14 days and with impairment of angiogenesis in the ulcer base. Lately, Kato & Takeuchi (2002) found that arthritic conditions alter the mucosal ulcerogenic and healing responses in the rat stomach. Administration of rofecoxib to arthritic rats provoked the gastric lesions, but did not cause any damage in normal rats. Gretzer et al (2001) reported that in the normal stomach, lesions develop only when both COX-1 and COX-2 are inhibited. On the contrary, during acid challenge, inhibition of COX-1 renders the mucosa more vulnerable, suggesting an important role of COX-1 in mucosal defence in the presence of potentially noxious agent. In this function, COX-1 is supported by COX-2. In the face of pending injury, however, COX-2 cannot maintain mucosal integrity when the activity of COX-1 is suppressed. Similar results have been observed by Tanaka et al (2001) and also very recently by the same group (Tanaka et al 2002a, b) in their studies conducted on rat stomach and intestine, altered by injury induced by indometacin. They found that gastrointestinal ulcerogenic properties of NSAIDs are not accounted for solely by COX-1 inhibition, but require the inhibition of both COX-1 and COX-2.

Similarly, Weaver et al (2001) have compiled case studies of 73 human fatalities reported with celecoxib and rofecoxib. Out of these fatalities, 37 involve rofecoxib and in many of these cases, the gastrointestinal events led to the patients' deaths. However, the authors could not conclude for sure about the gastrointestinal safety of these drugs as 77% of the patients had clinical history of gastrointestinal complications. In another reported study (Caroli & Monica 2001), a 77-year-old female with previous history of gastrointestinal complications was treated for OA with rofecoxib 25 mg and complained about haematemesis and melaena. Upper digestive endoscopy revealed multiple large erosions of the stomach with stigmata of recent haemorrhage. Thus, it was concluded by the authors that the administration of rofecoxib in altered gastrointestinal mucosa aggravated and complicated the gastric ulcers and necrosis in the small intestine, consequently restricting their clinical usage. A small number of cases on the occurrence of acute colitis, gastrointestinal bleeds, etc., have been reported in literature (de La Serna Higuera et al 2002; Foral et al 2002; Freedman et al 2002; Freitas et al 2002). Treatment with rofecoxib was associated with a significantly higher number of gastrointestinal events in patients with antibodies for Helicobacter pylori than in patients without these antibodies (Hochberg 2001). The treatment effect was, however, significant in both the subgroups. Finally, the incidence of gastrointestinal events remained low in rofecoxib-treated patients who lacked any risk factors for serious upper gastrointestinal events. However, Hawkey et al (2001b) reported that gastroduodenal erosion at baseline and a clinical history of upper gastrointestinal disease, but not H. pylori colonization, increased the risk for endoscopically detected ulcers and clinical bleeds. Therefore, it can be concluded that the risk of gastric toxicity with rofecoxib is governed by the presence of previous clinical gastrointestinal history.

Literature (Naesdal & Wilson 2001; Wolfe et al 2002) reports that concomitant use of traditional NSAIDs with antiulcer agents like misoprostol, proton pump inhibitors (PPIs) and H_2-receptor antagonists help in better prevention and healing of the gastroduodenal ulcers than observed with NSAIDs alone. Watson et al (2001) compiled data of gastrointestinal outcomes observed with rofecoxib in various OA clinical trials. The authors concluded that the rate of gastrointestinal co-medications was considerably lower in patient groups treated with rofecoxib (17.5%) than that observed in patients treated with comparator traditional NSAID (27.0%) ($P < 0.001$) over 12 months. Rofecoxib (12.5 mg) has been found to have similar efficacy and improved gastrointestinal tolerability as compared with Arthrotec (diclofenac 50 mg plus misoprostol 200 μg twice daily) (Acevedo et al 2001). There was significant reduction in the

incidence of diarrhoea ($P < 0.001$), NSAID-type gastrointestinal adverse effects ($P = 0.004$), as well as gastrointestinal adverse effects ($P < 0.001$). Also, the number of discontinuations due to overall clinical adverse effects was less with rofecoxib therapy than with Arthrotec ($P < 0.05$). Recently, Wolfe et al (2002) reported that the recipients of COX-2 inhibitors suffer with significantly fewer ulcers than the recipients of equivalent non-selective NSAIDs, regardless of concomitant PPI utilization. Hence with rofecoxib, the concurrent intake of antiulcer agents was found to be generally unnecessary but may be of use in patients with a high risk of gastrointestinal complications (Hunt et al 2002).

Mahadevan et al (2002) observed that COX-2 inhibitors like rofecoxib and celecoxib may be safe and beneficial in patients with irritable bowel diseases, whereas nonselective NSAIDs are relatively contraindicated for fear of disease aggravation. However, they recommend that a placebo-controlled trial should be conducted to confirm the observations found in their study.

By and large, analysis of endoscopic data and clinical PUB events pooled from several trials provide sufficient evidence that rofecoxib is associated with fewer clinically symptomatic ulcers and ulcer complications than reported with conventional NSAIDs (Hawkey 2001; Hawkey et al 2001a; Palmer 2001; Laine 2002; Peura 2002; Scheiman 2002). Hence, rofecoxib is recommended as first-line therapy for the symptomatic treatment of arthritic conditions in patients who are vulnerable to NSAID-associated gastrointestinal toxicity (Schnitzer & Hochberg 2002). However, this needs to be ratified by postmarketing surveillance. Despite the favourable gastrointestinal tolerability of rofecoxib, the US FDA still requires the packaging directions for rofecoxib to carry gastrointestinal ulcer warnings similar to the ones used for the traditional NSAIDs. Also, several medical scientists have shown serious concern about the concomitant therapy of selective COX-2 inhibitors like rofecoxib with low-dose aspirin in patients with cardiovascular risk, where the latter might negate the gastro-protection offered by the former (Brian 2001; Seibold & Spector 2001; Husni et al 2002; Loewen 2002; Olszynski et al 2002).

Tolerability: cardiovascular effects

Both COX-1 and COX-2 are involved in the production of prostaglandins and thromboxanes (Cleland et al 2001). In-vivo biochemical studies suggest that selective COX-2 inhibition could perturb the platelet-vascular homoeostasis mediated by a balance between the effects of thromboxane A_2 (TxA_2) and prostacyclin (PGI_2). TxA_2 is a vasoconstrictor and promotes platelet aggregation, whereas PGI_2 is a vasodilator and inhibits platelet aggregation. Thus, these drugs may permit thrombosis, as they inhibit endothelial cell production of PGI_2 but not the production of TxA_2 by platelets (Catella-Lawson & Crofford 2001; Cleland et al 2001; FitzGerald & Patrono 2001; Mukherjee 2002). Therefore, cardiovascular safety is an area of concern for the COX-2 selective inhibitors (Crofford 2002; Konstam & Weir 2002; Pedros et al 2002; Schoors 2002).

Ingestion of either celecoxib or rofecoxib by healthy subjects has been reported to suppress PGI_2 production in-vivo, measured through its urinary metabolite, with no effect on platelet TxA_2 production (Catella-Lawson et al 1999; Cleland et al 2001). In a retrospective analysis of the cardiovascular events conducted in the rofecoxib OA phase IIb/III trials ($n = 5435$), no difference was found between rofecoxib, comparator non-selective NSAIDs (ibuprofen, diclofenac or nabumetone) and placebo (Reicin et al 2002). The cardiovascular events included myocardial infarction, angina pectoris, transient ischaemic attack, deep vein thrombosis and peripheral thrombosis. The incidence of thrombotic cardiovascular adverse effects was 1.93 per 100 patient-years in the rofecoxib treatment group as compared with 2.27 per 100 patient-years in the combined non-selective NSAID group. In the trials that compared rofecoxib with placebo, the incidence of thrombotic cardiovascular adverse effects was 2.71 per 100 patient-years in the rofecoxib treatment group as compared with 2.57 per 100 patient-years in the placebo group. Antiplatelet trialist's collaboration (APTC) end point is a widely accepted indicator of overall cardiovascular impact of antithrombotic compounds evaluated in clinical trials. This end point summarizes the morbid and fatal sequelae of atherosclerosis, as well as the fatal haemorrhagic sequelae that may accompany therapy with antiplatelet agents (Konstam et al 2001). Consistent with the risks of cardiovascular adverse effects, similar rates of APTC events were reported with rofecoxib, placebo and comparator non-selective NSAIDs (Reicin et al 2002).

Among all the randomized controlled trials performed to date with rofecoxib, only the VIGOR study depicted a significant difference between rofecoxib (50 mg) and its active comparator (naproxen 550 mg) in the risk of thrombotic events (Bombardier et al 2000). The protocol prohibited the use of aspirin or other antiplatelet and anticoagulant medications. The study demonstrated that a supratherapeutic dose of rofecoxib was associated with a four-fold increase in the rate of myocardial infarction (0.4%) compared with naproxen (0.1%), with relative risk of 0.2 (CI: 0.1, 0.7). The authors suggested that these data could be consistent with the theory that regular use of naproxen may have a cardioprotective effect similar to that of aspirin, because of the inhibition of platelet aggregation throughout the dosing interval. Alternatively, rofecoxib at dose of 50 mg once daily could have prothrombotic effects, especially in the absence of concomitant COX-1 inhibition in the patients with increased risk of thrombosis.

Further, a meta-analysis of phase IIb-V rofecoxib clinical trials in over 28 000 patients, with over 14 000 patient-years at risk, failed to show any significant differences in the risk for serious cardiovascular thromboembolic outcomes between the patients taking rofecoxib and those taking non-naproxen nonselective NSAIDs or placebo (Konstam et al 2001). The relative risk for an APTC endpoint was 0.84 (95% CI: 0.51, 1.38) when comparing rofecoxib with placebo, 0.79 (95% CI: 0.40, 1.55) when comparing with the studied non-naproxen NSAIDs and 0.69 (95% CI: 1.07, 2.69) when comparing with naproxen.

However, the vast majority of patients taking rofecoxib in the meta-analysis received doses of either 12.5 or 25 mg once daily. Thus, one can not completely exclude a possible prothrombotic effect of this long half-life COX-2 selective inhibitor in VIGOR analysis, when taken at higher than recommended dosages for a prolonged period in the absence of COX-1 inhibition.

A separate 7-day study investigated the effects of rofecoxib (25 mg per day) versus naproxen (750 mg per day) on endothelial function in healthy subjects (n = 35) (Verma et al 2001). Vascular response was measured using forearm strain-gauge plethysmography. Changes in forearm blood flow (FBF) in response to the endothelium-dependent vasodilator acetylcholine (ACh; 3, 10, and 30 $\mu g\,min^{-1}$) and the endothelium-independent vasodilator sodium nitroprusside (1 and 10 $\mu g\,min^{-1}$) were assessed before and after treatment. Treatment did not result in any change in ACh-mediated increase in FBF, in either the naproxen group ($P = 0.27$) or the rofecoxib group ($P = 0.58$). Similarly, there was no change in FBF in either group in response to sodium nitroprusside ($P = 0.55$ for naproxen, $P = 0.63$ for rofecoxib). Hence, when used in doses proven to inhibit PGI_2 production in healthy individuals, rofecoxib did not result in changes in endothelium-dependent vasodilatation, or in blood pressure. However, the effect of rofecoxib on vasodilator response in patients with coronary artery disease needs to be investigated.

On the whole, it has been advised that rofecoxib should not be used alone in patients with serious cardiovascular thrombotic events, especially with myocardial infarction (Adelman 2001; Mukherjee et al 2001; Peretz 2001; Frankish 2002; Graham et al 2002; Jaeschke et al 2002; Schoors 2002). Either low-dose aspirin or another antiplatelet agent should be given in conjunction with this drug. However, no studies have been reported on the gastrointestinal tolerability with concomitant use of such combinations along with rofecoxib.

Tolerability: renal effects

Both COX-1 and COX-2 are constitutively expressed in the renal tissues of all the species. COX-2 is known to be localized to the renal vasculature, the cortical macula densa and the medullary interstitial cells of the kidney, and its content in these areas increases with age (Harris et al 1994; Jensen & Kurtz 1997; Kömhoff et al 1997; Cheng et al 1999; Ferguson et al 1999; Ferreri et al 1999; Brater et al 2001; FitzGerald & Patrono 2001; Kammerl et al 2001b). In contrast, COX-1 is found in vasculature, collecting ducts and thin loop of Henle (Harris et al 1994; Brater et al 2001; FitzGerald & Patrono 2001; Perazella & Tray 2001). COX-2 can be upregulated in a number of experimental settings, such as sodium restriction, volume depletion, partial renal ablation, renal artery stenosis and active lupus nephritis (Harris et al 1994; Jensen & Kurtz 1997; Kömhoff et al 1997; Brater et al 2001). COX-2 dependent prostaglandins are necessary for normal renal development (Brater et al 2001; FitzGerald & Patrono 2001; Kammerl et al 2001). In mice, complete absence of COX-2 results in severe renal dysplasia characterized by a postnatal arrest of maturation in the subcapsular nephrogenic zone and progressive deterioration with increasing age (Dinchuk et al 1995). Antenatal exposure of both mice and rats to an inhibitor of COX-2, but not of COX-1, has also been found to have similar effects (Kömhoff et al 2000). Accordingly, it has been speculated by many researchers that COX-2 inhibitors share a similar risk of adverse effects on the renal function to the nonselective NSAIDs (Catella-Lawson et al 1999; Cannon et al 2000; Chiolero 2000; Swan et al 2000; Brater et al 2001; Deray 2001; FitzGerald & Patrono 2001; Perazella & Tray 2001; Whelton 2001; Gertz et al 2002; Harris 2002). Between the two coxibs (i.e., celecoxib and rofecoxib), the former has been reported by a few researchers to have much safer renal profile than the latter (Zhao et al 2001; Osterhause et al 2002). However, the latest search by the US FDA's Adverse Event Reporting System (AERS) states that both coxibs are associated with renal effects similar to that of conventional nonselective NSAIDs (Ahmad et al 2002).

Data on the renal safety profile of rofecoxib are available from various sources and have been compiled in a classified manner, as listed below.

Effects on renal prostaglandins The urinary levels of 6-keto $PGF_{1\alpha}$ (the stable metabolite of PGI_2) and PGE_2 are documented to reflect the renal synthesis of PGI_2 and PGE_2, respectively (Froelich et al 1975; Catella et al 1986). In healthy elderly adults (mean age 65–68 years), rofecoxib (50 mg daily) produced a 47% decrease from baseline in urinary 6-keto $PGF_{1\alpha}$, a value comparable in magnitude to that observed with indometacin (53%) (Catella-Lawson et al 1999). In a separate study, rofecoxib, at doses of 12.5 and 25 mg once daily, reduced urinary PGE_2 and 6-keto $PGF_{1\alpha}$ excretion in healthy subjects by about 40–50%, the reduction being similar to that seen following administration of meloxicam (15 mg daily) or diclofenac (50 mg three times daily) (Van Hecken et al 2000). In animals, rofecoxib has been found to decrease the plasma levels of 6-keto $PGF_{1\alpha}$ both in normotensive and spontaneously hypertensive rat strains fed on either normal or high-salt diet (Hocherl et al 2002a). Accordingly, these investigations also support the hypothesis that the COX-2 isoform plays an important role in renal prostaglandin biosynthesis.

Effects on renal physiology: glomerular filtration rate (GFR) and sodium excretion In elderly subjects (60–80 years) on a sodium-replete diet (200 mEq daily), 50 mg rofecoxib did not produce any significant alteration in GFR after 2 weeks of treatment, whereas indometacin (50 mg three times daily) resulted in a 5% decrease from baseline ($P < 0.05$) (Catella-Lawson et al 1999). Both drugs produced similar transient and clinically insignificant reduction in urinary sodium excretion during the first 3 days of treatment. The findings of this study suggested that COX-2 inhibition results in sodium retention, while the decline in GFR is attributable to the blockade of COX-1. A subsequent study (Swan et al 2000) indicated

that, under different clinical circumstances, COX-2 inhibition could affect both solute homoeostasis and renal haemodynamics. In a double-blind, multiple-dose, placebo-controlled, parallel-group study in geriatric patients (65–80 years) with mild renal impairment (mean creatinine clearance 65 mL min^{-1}), stabilized on low-sodium diet (30 mEq daily), rofecoxib (250 mg once daily) and indometacin (75 mg once daily) produced a decrease in GFR by 0.23 mL s^{-1} ($P < 0.001$) and 0.18 mL s^{-1} ($P = 0.003$), as compared with placebo. On the other hand, a respective decrease in GFR of 0.14, 0.13 and 0.10 mL s^{-1} was observed after multiple dosing of rofecoxib at a dose of 12.5 mg per day ($P = 0.019$) and 25 mg per day ($P = 0.029$), and of 50 mg three times daily indometacin ($P = 0.086$), indicating that all the three treatments had almost similar effect on GFR. However, there were no consistent changes in urinary sodium or potassium excretion in rofecoxib-treated subjects. While rofecoxib 12.5 mg produced a significant 34.6% reduction in peak urinary sodium excretion as compared with placebo ($P < 0.05$), no significant effect was observed in subjects receiving either rofecoxib 25 mg (22.8%) or indometacin (25.5%). Unfortunately, the compliance with the sodium-restricted diet was not documented in this trial. Nonetheless, this study showed definite effects of a COX-2 inhibitor on renal haemodynamics similar to those with a nonselective NSAID. Decreased sodium excretion can result in weight gain, peripheral oedema, attenuation of the effects of antihypertensive agents and, rarely, precipitation of chronic heart failure (Brater 1999). In a very recent study, administration of rofecoxib (25 mg per day) for two weeks in patients with OA produced a significant increase in serum sodium levels ($P < 0.05$) and in body weight ($P < 0.001$) (Niccoli et al 2002). Although most findings reveal a negative impact of rofecoxib on sodium–water excretion, some latest reviews (Ahmad et al 2002; Harris 2002) state that these effects are quite similar to those with nonselective NSAIDs.

Effects on renal physiology: incidence of peripheral oedema As with nonselective NSAIDs, both rofecoxib and celecoxib have been reported to cause peripheral oedema (Brater et al 2001; Zhao et al 2001; Graham et al 2002; Osterhause et al 2002). In one study (Cannon et al 2000) carried out in 784 patients with OA, lower-extremity oedema was reported in 3.9% and 1.9% of the patients treated with 12.5 or 25 mg of rofecoxib, respectively. The incidences were found to be similar to those observed in patients receiving diclofenac 50 mg three times daily (3.4%), but higher than those observed in placebo-treated patients (1%). In the VIGOR trial, the incidence of renal adverse effects was low, yet similar among the two patient groups receiving different drug treatment (i.e., rofecoxib (1.2%) and naproxen (0.9%)) (Bombardier et al 2000). Discontinuations due to oedema-related adverse events were numerically higher in the rofecoxib group ($n = 25$) than in naproxen-treated patients ($n = 13$) (FDA 2002b). A somewhat higher incidence of peripheral oedema (6.3%) was observed with 50 mg rofecoxib; this dose, however, is neither approved nor required for maximal efficacy during chronic use.

Of the two coxibs, Whelton et al (2001) found that in a 6-week, randomized, double-blind trial, conducted in elderly hypertensive patients with OA of the hand, hip or knee ($n = 811$; age > 65 years), significantly higher oedema ($P = 0.014$) developed in patients treated with 25 mg of rofecoxib (9.5%) than with 200 mg of celecoxib (4.9%). A randomized, double-blind, placebo-controlled comparative study on rofecoxib (25 mg once daily) and celecoxib (200 mg once daily) in 1082 patients with OA of the hip or knee, failed to demonstrate a difference in the proportion of patients with clinically significant increases either in systolic or diastolic blood pressure between the two coxibs. Significant differences however, were found between the patient groups receiving coxibs and the placebo (Geba et al 2001). Nonetheless, the authors advised that caution must be exercised when interpreting these results, as the half-lives of these coxibs differ and that the trial may not have used comparably efficacious doses.

Effects on renal physiology: blood pressure Mean systolic and diastolic blood pressures have been found to remain constant over an entire year of rofecoxib treatment, with clinically insignificant mean changes from baseline values in comparison with diclofenac 50 mg three times daily (Cannon et al 2000). Mean changes in blood pressure (systolic and diastolic) in patients treated with once-daily doses of rofecoxib (12.5 or 25 mg) for over a 1-year period were ≤ 1 and ≤ 3 mmHg, respectively. These findings indicate that clinically insignificant alteration in diastolic or systolic blood pressure should be anticipated if the patients are switched from a nonselective NSAID to these doses of rofecoxib (Brater et al 2001). However, hypertension has been reported in some patients as an adverse effect. Over a 6-month treatment period, 0.1% of the patients receiving either 12.5 or 25 mg rofecoxib discontinued therapy owing to hypertension, as compared with 0.4% of the ibuprofen-treated patients. However in the VIGOR study ($n \sim 8000$), the number of discontinuations due to increase in blood pressure was significantly higher in patients treated with rofecoxib, as compared with naproxen (28 vs 6; relative risk: 4.67; CI: 1.93, 11.28) (FDA 2002b). In a 6-week study reported by Whelton et al (2001), in addition to oedema, there was significantly higher increase ($P = 0.032$) in the systolic blood pressure in rofecoxib-treated patients (17%) than in celecoxib-treated patient group. Also, the diastolic blood pressure was found to elevate in 2.3% of rofecoxib recipients in comparison with 1.5% of celecoxib recipients ($P = 0.44$). At week 6, the change from baseline in mean systolic blood pressure was +2.6 mmHg for the rofecoxib-treated group in comparison to −0.5 mm Hg for the celecoxib-treated group ($P = 0.007$). Thus, preferably, the patients receiving rofecoxib therapy should be monitored for the development of cardiorenal events. Niccoli et al (2002) report that rofecoxib 25 mg daily, when administered in patients with OA for two weeks, produced a significant increase in systolic and diastolic blood pressure

($P < 0.001$). However, Reitblat et al (2002) have observed that treatment with rofecoxib 25 mg did not cause any change in arterial blood pressure during day time but caused an increase in night-time systolic and diastolic blood pressure. In a separate 6-week study, rofecoxib (12.5 and 25 mg once daily) produced renal adverse effects such as oedema, hypertension and weight gain similar to ibuprofen (2400 mg daily), indicating that rofecoxib is similar to a non-selective NSAID in terms of effects on blood pressure. However, some authors have suggested that the therapy with rofecoxib needs to be monitored (Frishman 2002; Osterhaus et al 2002).

Effects on renal physiology: serum creatinine and serum electrolyte levels Following prolonged administration for over one year, rofecoxib (12.5 or 25 mg) produced only a trivial change in serum creatinine levels in patients with OA (Cannon et al 2000). After six months, the mean change from baseline in serum creatinine was observed to be 0.03 mg dL^{-1} with rofecoxib (25 mg), similar to that observed with NSAID comparators ibuprofen and diclofenac (0.02 mg dL^{-1} in each case) and somewhat greater than that observed with placebo (-0.02 mg dL^{-1}). Fewer rofecoxib-treated patients discontinued therapy due to elevation in serum creatinine as compared with the patients treated with the nonselective NSAID (0.06 vs 0.26%).

Rofecoxib may result in a modest degree of hyperkalaemia, presumably as a result of hyporeninaemic hypoaldosteronism, similar in magnitude and frequency to that observed in patients receiving comparator NSAIDs (Brater 1999; Brater et al 2001; Hocherl et al 2002b). In a 6-week OA study, 2%, 3.2%, 3.2%, 1.7% and 6.1% of patients were found to have potassium concentrations exceeding the predefined limits (≥ 0.8 mEq L^{-1}) on one or more occasions in the placebo, rofecoxib 12.5 mg, rofecoxib 25 mg, ibuprofen 2400 mg and nabumetone 1500 mg groups, respectively (Brater et al 2001). However, $\leq 0.1\%$ of the patients receiving rofecoxib (12.5–25 mg once daily) had serum potassium concentrations > 5.5 mEq L^{-1} on two or more occasions, as compared with 0.3% of the patients on placebo.

Results of all the studies described above provide some insight into their potential nephrotoxicity. However, the subjects who were investigated were generally healthy with minimal risk of serious NSAID-associated nephrotoxicity. The findings of these studies suggested that the selective COX-2 inhibitors have the potential to disrupt renal physiology (i.e., renal blood flow, GFR and excretion of sodium, potassium and water), but the effects are minor and clinically insignificant. In contrast, a few case reports (Wolf et al 2000; Ofran et al 2001; Perazella & Tray 2001; Rocha & Fernandez-Alonso 2001; Wahba & Soper 2001; Woywodt et al 2001; Hay et al 2002) published in literature provide a brief account of the potential nephrotoxicity of rofecoxib. Perazella & Tray (2001) reported 14 cases of renal toxicity associated with the use of coxibs. By and large, in all these cases, patients had several risk factors for NSAID-induced nephrotoxicity, including chronic renal insufficiency, cardiac disease with impaired ventricular function, diabetes mellitus, diuretic and ACE inhibitor therapy, vascular disease, hypertension and volume-depleted states. Taken together, all the findings reveal that rofecoxib, like nonselective NSAIDs, can cause acute renal impairment in patients with risk factors. Therefore in patients with risk factors for nephrotoxicity, it is prudent to approach rofecoxib therapy cautiously and in a fashion analogous to that with traditional NSAIDs (Chiolero et al 2000; Ahmad et al 2002; Brater 2002; Noroian & Clive 2002). Further, it has been advised that rofecoxib should not be prescribed to patients with advanced renal disease (Ahmad et al 2002; Kitahara et al 2002).

Tolerability: hepatic effects
In controlled clinical trials of rofecoxib, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable with that observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking rofecoxib (12.5 or 25 mg) and 0.1% of patients taking placebo had notable elevations of alanine aminotransferase or aspartate aminotransferase (Merck & Co. 1998). Use of rofecoxib is, therefore, not recommended in patients with moderate or severe hepatic insufficiency. Hence, it is advisable that on the appearance of any signs and symptoms of liver disease, the use of rofecoxib should be discontinued.

Adverse effects
Rofecoxib is generally well tolerated (Matheson & Figgitt 2001). It has been considered to be safe when administered at therapeutic doses for periods as long as 6–12 months. Adverse events occurring in at least 2% of the patients receiving rofecoxib in nine controlled OA studies between 6 weeks and 6 months duration were observed to be abdominal pain, dizziness, pedal oedema, upper respiratory tract infection and fatigue in general (Merck & Co. 1998). Hypertension, nausea, dyspepsia, diarrhoea, epigastric discomfort and heartburn related to the cardiovascular system and gastrointestinal tract were also observed. Headache, back pain and urinary-tract infection were some of the other side effects reported. Isolated reports on the occurrence of aseptic meningitis, acute pancreatitis, paraesthesia, fixed drug eruptions, aquagenic wrinkling of palms, sinusitis, urticaria, angioedema, haemorrhagic pulmonary oedema, erythema multiforme and cholestatic hepatitis with rofecoxib have also been observed (Kaur et al 2001; Kelkar et al 2001; Amaravadi et al 2002; Block 2002; Bonnel et al 2002; Carder & Weston 2002; Daugherty & Gora-Harper 2002; Huster et al 2002; Kumar et al 2002). No serious toxicity has been reported following the single-dose administration of rofecoxib even at the very high dose of 1000 mg and multiple high doses of 250 mg daily for up to 14 days. Very recently, Bannwarth et al (2003) evaluated the safety profile of rofecoxib in patients with OA ($n = 2896$) in a 24-week, open-label, non-pharmacological intervention trial. Closely monitoring the patients for any incidence of

adverse effects, the scientists concluded that the drug is associated with a low rate of serious adverse events in patients with OA.

Contraindications and precautions

Rofecoxib is contraindicated in patients with known hypersensitivity to the drug or any of the components of its dosage form (Merck & Co. 1998). Although rofecoxib has been reported to be well-tolerated and safe in patients with aspirin-sensitive asthma (Stevenson & Simon 2001; Szczeklik et al 2001; Martin-Garcia et al 2002) and aspirin- or NSAID-sensitive allergic reactions (Enrique et al 2000; Berges-Gimeno et al 2001; Hinrichs et al 2001; Sanchez Borges et al 2001; Nettis et al 2002; Pacor et al 2002; Quiralte et al 2002), it has nevertheless been recommended by the manufacturer that it should not be administered to patients who have clinical history of asthma, nasal polyps, urticaria or who have had allergic-type reactions after taking aspirin or other NSAIDs (Merck & Co. 1998). In placebo-controlled trials, no significant difference was observed between rofecoxib and placebo in clinical reports of anaemia. Nevertheless, the patients receiving long-term treatment with rofecoxib should have their haemoglobin and haematocrit levels monitored if they exhibit any signs or symptoms of anaemia or blood loss. Rofecoxib does not usually affect platelet counts, prothrombin time, partial thromboplastin time or platelet aggregation at the indicated dosages. However, it has been advised by several workers (Merck & Co. 1998; Atkinson 2002; Noroian & Clive 2002; Brater 2002; Frankish 2002; Graham et al 2002) that rofecoxib should be used with caution, and in the lowest recommended dose, in patients with fluid retention, hypertension or heart failure.

Rofecoxib, when administered to healthy women, has been reported to have a negative local effect on human ovulation, resulting in delayed follicular rupture (Pall et al 2001). No reports are available regarding the effect of rofecoxib in women during pregnancy or lactation. However in animal studies, rofecoxib has been shown to cross the placental barrier (Merck & Co. 1998; Halpin et al 2000). Rofecoxib has been observed to produce peri-implantation and postimplantation losses and reduced the embryo/foetal survival in rats and rabbits after oral doses of 10 and 75 mg kg^{-1} daily, respectively (Merck & Co. 1998). The researchers have attributed these changes to the inhibition of prostaglandin synthesis and not to the alteration of female reproductive function. Hence, the manufacturer suggests that rofecoxib should be used in pregnant women only when the benefit overweighs the potential risk. Also, its use in late pregnancy is not advised because of the likelihood of premature closure of the ductus arteriosus. Since the drug is excreted in animal milk, its use in nursing mothers is also not recommended (Merck & Co. 1998). When administered to rabbits, some incidences of vertebral malformations were observed, however, the frequency was statistically insignificant. At doses up to 50 mg kg^{-1} daily (approximately 28- and 10-fold higher than human exposure at 25 and 50 mg daily based on AUC_{0-24}), rofecoxib was not found to be teratogenic in rats. Also, no carcinogenic or mutagenic effect has been observed with rofecoxib.

Dosage and administration

Rofecoxib is administered orally and is available in the form of tablets (12.5 and 25 mg) and suspension (each 5 mL contains 12.5 mg of rofecoxib) (Merck & Co. 1998). In OA and RA, the recommended starting dose of rofecoxib is 12.5 mg once daily, which can be increased up to the maximum recommended dose (25 mg). Rofecoxib 50 mg once daily is the recommended initial dose for the management of acute pain and treatment of primary dysmenorrhoea. Rofecoxib tablets may be taken with or without food.

Future prospects

During recent years, multidisciplinary studies in epidemiology and molecular biology, as well as preclinical studies, have contributed significantly to understanding the aetiology of carcinomas. The epidemiological and laboratory studies suggest that COX-2 levels are upregulated in various pathophysiological conditions like polyposis (Boolbol et al 1996), gastric cancer (Ristimaki et al 1997), colon and colorectal carcinoma (Eberhart et al 1994), neuroectodermal tumour (Patti et al 2002) and Barrett's oesophagus (Wilson et al 1998).

Based on these findings, research has been going on to investigate the potential role of COX-2 inhibitors in the prevention, as well as treatment, of colon, skin and bladder cancer, and polyposis (Ziegler 1999; Kalgutkar & Zhao 2001; Reddy & Rao 2002). In this regard, the US FDA has already approved one of the coxibs (celecoxib, 400 mg twice daily) for use in reducing the number of adenomatous polyposis (FDA 1999b). Oshima et al (2001) reported that rofecoxib can inhibit polyposis in Apcdelta 716 mouse. Analogously, Lew et al (2002) also observed that rofecoxib, together with adenomatous polyposis coli gene, can reduce the polyp formation by 87%. These findings suggest that rofecoxib can be used as a potential chemopreventive agent in human intestinal and colorectal cancer. Rofecoxib has already been indicated as a supportive therapy with epidermal growth factor receptor kinase inhibitor in colorectal cancer (Frost & Discafani-Marro 2002). Of late, Kaur et al (2002) investigated the role of rofecoxib (25 mg once daily) in Barrett's oesophagus. During the disease, the levels of COX-2, PGE_2 and proliferating cell nuclear antigen were 2- to 3-times higher at baseline than those observed in normal oesophagus and duodenum. Following rofecoxib therapy for 10 days, the levels of these biochemicals were considerably reduced ($P < 0.005$). The PPIs were maintained throughout the study. Therefore, the researchers have suggested that rofecoxib, along with acid-suppressive therapy, may be a promising chemopreventive agent against dysplasia and oesophageal adenocarcinoma. Fraley et al (2002) reported that rofecoxib could be effectively combined with tyrosine kinase inhibitors for the treatment of angiogenesis. Further, Dicker et al (2001) suggested that the combination of rofecoxib and radiation acts as a

complimentary strategy with clinical ramifications to target angiogenesis-dependent malignancies.

Literature is replete with reports indicating that the COX-2 enzyme is overly expressed in the microglia of cognitive centres within the hippocampus and cortex in Alzheimer's disease (Blain et al 2000; Ferencik et al 2001; Jain et al 2002). As a consequence, long-term administration of anti-inflammatory drugs is likely to have a protective effect on the onset of Alzheimer's disease. Coxibs may have an advantage over traditional NSAIDs as they can decrease the excessive expression of COX-2 selectively with better gastrointestinal tolerability. These agents also decrease the excessive activation of some transcription factors responsible for the initiation of transcription of a number of pro-inflammatory genes (Ferencik et al 2001). The selective inhibitors of COX-2 thereby can have an anti-inflammatory effect, operating at several levels. Recently, Aisen (2002) reported that a multicentre, double-blind, placebo-controlled trial is being conducted by the Alzheimer's Disease Cooperative Study to determine the effect of rofecoxib or naproxen in retarding the rate of cognitive and clinical decline in Alzheimer's disease. However, this study is currently underway and the outcome(s) will determine the utility of selective and non-selective COX inhibitors for the prevention and treatment of Alzheimer's disease. Block & Lines (2002) also lately reported that rofecoxib can be co-administered with γ-aminobutyricacid-sub-A-α-5-inverse agonist for the treatment of Alzheimer's disease. However, the use of NSAIDs in Alzheimer's disease was pioneered by the work of McGeer & McGeer (1995). Besides COX-1 and COX-2, the authors have indicated the role of many other inflammatory stimulators involved in neuroinflammation in Alzheimer's disease-like beta-amyloid protein; the pentraxins C-reactive protein and amyloid P; complement proteins; interleukin-1, interleukin-6 and tumour necrosis factor-alpha; the protease inhibitors alpha-2-macroglobulin and alpha-1-antichymotrypsin. Hence, as there are a number of diverse inflammatory targets that can be acted upon by conventional NSAIDs, the superiority of coxibs over them needs to be investigated critically.

Rofecoxib is also being investigated for other pathophysiological conditions like atherosclerosis, hyperprostaglandin E syndrome/antenatal Bartter syndrome (HPS/aBS) and Gitelman's syndrome. Burleigh et al (2002) reported that COX-2 enzyme promoted atherosclerotic lesion formation in low-density lipoprotein receptor-deficient mice and that treatment with rofecoxib or indometacin for 6 weeks resulted in a considerable reduction in the early lesion formation (25% and 37%, respectively). This observation supports the high potential of anti-inflammatory approaches to the prevention of atherosclerosis.

Reinalter et al (2002), in their study conducted on patients with HPS/aBS, observed upregulation of COX-2 enzyme and found that HPS/aBS-associated hyperreninaemia and the salt depletion in patients is dependent upon the COX-2 levels. Hence, the use of rofecoxib may be promising in such conditions (HPS/aBS, Gitelman's syndrome) (Mayan et al 2002; Reinalter et al 2002). Rofecoxib holds tremendous promise in treating and mitigating neurological ailments like hemicrania continua (Peres & Zukerman 2000; Peres & Silberstein 2002) and migraine (Krymchantowski & Barbosa 2002; Simitchieva et al 2002) and for pain management in osteoid osteoma (Bottner et al 2001).

Conclusions

Rofecoxib is a novel anti-inflammatory agent with a biochemical and pharmacological profile vividly distinct from that of conventional NSAIDs. It possesses an extremely high affinity for selective inhibition of COX-2 with no effect on the COX-1 isoenzyme. Besides its high degree of anti-inflammatory and analgesic activity, rofecoxib exhibits excellent antipyretic potential with a highly favourable gastrointestinal tolerability. Rofecoxib has been documented to be efficacious in the symptomatic treatment of OA, RA, acute pain and primary dysmenorrhoea. Numerous clinical trials demonstrate the therapeutic efficacy of rofecoxib to be better than, or at least similar to, that observed with comparator non-selective NSAIDs, and unambiguously superior to that of placebo (Zacher & Schattenkirchner 2002). In comparison with celecoxib, another coxib, it portrays better efficacy in the treatment of osteoarthritis and dental pain.

The latest surveys report that rofecoxib shares similar risk of renal and thrombotic events as observed with non-naproxen non-selective NSAIDs. Owing to its good gastrointestinal tolerability, rofecoxib is considered to be a safer option in the high-risk patients (i.e., patients with history of gastrointestinal complications, patients taking high doses of NSAIDs, corticosteroids or alcohol or elderly patients aged over 65 years) (Hawkey 2001; Rajadhyaksha & Dahanukar 2001; Weaver 2001; Bombardier 2002; Crofford 2002; Lanas 2002; McMurray & Hardy 2002; Steinfeld & Bjorke 2002). Despite being relatively more expensive than many popular non-selective NSAIDs, therapy with rofecoxib is considered to be more effective and cost-effective in these patients, as it obviates the need for other concomitant therapies like H_2-receptor blockers, PPIs, etc. (Hilson & Furst 2000; Marshall et al 2001; Schnitzer 2001; Fendrick 2002; Katz 2002; McMurray & Hardy 2002). However, in case of concomitant use with low-dose aspirin in patients with cardiovascular risk, various experts suggest the intake of gastroprotective agents like PPIs.

The extent of bioavailability of rofecoxib is nearly 100% at lower doses. At higher doses, however, its absorption is slow and incomplete ostensibly due to its poor aqueous solubility. The drug has widely varying t_{max} values (2–9 h) indicating inconsistencies in the kinetics of absorption. Rofecoxib is eliminated predominantly by hepatic metabolism (majorly by cytosolic reductases), with little unchanged drug excreted in urine. Ample pharmacokinetic and pharmacodynamic investigations suggest that rofecoxib does not interact significantly with many other drugs.

Sizable numbers of reports have been published on the quantitative estimation of drug in biological fluids and in

pharmaceutical dosage forms. Regarding formulation aspects of rofecoxib, various dosage forms like oral fast melt tablets, clear oil preparations, topical/transdermal gels, microemulsions and multilayered tablets have been formulated with fruition. The aqueous solubility of rofecoxib has been improved using approaches like inclusion complexation, solid dispersions and formation of porous matrices. As rofecoxib in the dissolved state tends to pose stability problems with light and alkali, caution must be exercised in formulating and handling its solution dosage forms.

Based upon various literature findings, the drug seems to have a lot of promise futuristically as supportive therapy in Alzheimer's disease, polyps, Barrett's oesophagus, colon carcinomas, Bartter and Gitelman diseases and atherosclerosis. Nevertheless, further studies are required to investigate its superiority over other anti-inflammatory agents in these pathophysiological states.

References

Acevedo, E., Castaneda, O., Ugaz, M., Beaulieu, A. D., Pons-Estel, B., Caeiro, F., Casas, N., Garza-Elizondo, M., Irazoque, F., Hinojosa, W., Gutierrez-Urena, S., Vandormael, K., Rodgers, D. B., Laurenzi, M. (2001) Tolerability profiles of rofecoxib (Vioxx) and Arthrotec. A comparison of six weeks treatment in patients with osteoarthritis. Scand. J. Rheumatol. 30: 19–24

Adelman, A. (2001) Is rofecoxib safer than naproxen? J. Fam. Pract. 50: 204

Afflitto, L. (2000) Selective COX-2 inhibitors and the surgical patient. Plast. Surg. Nurs. 20: 91–93

Ahmad, S. R., Kortepeter, C., Brinker, A., Chen, M., Beitz, J. (2002) Renal failure associated with the use of celecoxib and rofecoxib. Drug Saf. 25: 537–544

Aisen, P. S. (2002) Evaluation of selective COX-2 inhibitors for the treatment of Alzheimer's disease. J. Pain Symptom Manage. 23 (Suppl. 4): S35–S40

Ajithadas, A., Anusuya, P., Balamarriapan, C., Lakshamanan, M. K., Nanjappan, K., Kumar, P. A. R. (2001) Reverse phase high performance liquid chromatographic determination of rofecoxib in tablets. Indian Drugs 38: 523–525

Akaraserennont, P., Mitchell, J. A., Appleton, I., Thiemermann, C., Vane, J. R. (1994) Involvement of tyrosine kinase in the induction of cyclooxygenase and nitric oxide synthase by endotoxin in cultured cells. Br. J. Pharmacol. 113: 1522–1528

Amaravadi, R. K., Jacobson, B. C., Solomon, D. H., Fischer, M. A. (2002) Acute pancreatitis associated with rofecoxib. Am. J. Gastroenterol. 97: 1077–1078

Aravind, M. K., Prescilla, R., Ofenstein, J. P. (2002) A rapid and sensitive high-performance liquid chromatography assay for rofecoxib in human serum. J. Chromatogr. Sci. 40: 26–28

Aristo Pharmaceuticals Limited (2000) Introducing Rofib India's first rofecoxib with the beta cyclodextrin advantage: a scientific brief. Aristo Pharmaceuticals Limted, Mumbai, India

Atkinson, H. G. (2002) COX-2 inhibitors: better than traditional NSAIDs? Vioxx and Celebrex may be no less risky than NSAIDs. Health News 8:5

Baillie, T. A., Halpin, R. A., Matuszewski, B. K., Geer, L. A., Chavez-Eng, C. M., Dean, D., Braun, M., Doss, G., Jones, A., Marks, T., Melillo, D., Vyas, K. P. (2001) Mechanistic studies on the reversible metabolism of rofecoxib to 5-hydroxyrofecoxib in the rat: evidence for transient ring opening of a substituted 2-furanone derivative using stable isotope-labeling techniques. Drug Metab. Dispos. 29: 1614–1628

Bannwarth, B., Treves, R., Euller-Ziegler, L., Rolland, D., Ravaud, P., Dougados, M. (2003) Adverse events associated with rofecoxib therapy: results of a large study in community-derived osteoarthritic patients. Drug Saf. 26: 49–54

Barden, J., Edwards, J. E., McQuay, H. J., Moore, R. A. (2002) Single-dose rofecoxib for acute postoperative pain in adults: a quantitative systematic review. BMC Anesthesiol 2: 4

Bekker, A., Cooper, P. R., Frempong-Boadu, A., Babu, R., Errico, T., Lebovits, A. (2002) Evaluation of preoperative administration of the cyclooxygenase-2 inhibitor rofecoxib for the treatment of postoperative pain after lumbar disc surgery. Neurosurgery 50: 1053–1057

Bellamy N. (1995) Outcome measurement in osteoarthritis clinical trials. J. Rheumatol. 22: 49–51

Bellamy, N., Buchanan, W. W., Goldsmith, C. H., Campbell, J., Stitt, W. L. (1988) Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J. Rheumatol. 15: 1833–1840

Berg, J., Christoph, T., Widerna, M., Bodenteich, A. (1997) Isoenzyme specific cyclooxygenase inhibitors: a whole cell assay system using the human erythroleukemic cell line HEL and the human monocytic cell line mono mac 6. J. Pharmacol. Toxicol. Methods 37: 179–186

Berges-Gimeno, M. P., Camacho-Garrido, E., Garcia-Rodriguez, R. M., Alfaya, T., Martin Garcia, C., Hinojosa, M. (2001) Rofecoxib safe in NSAID hypersensitivity. Allergy 56: 1017–1018

Berti, M., Danelli, G., Albertin, A., Deni, F., Moizo, E., Muzzolon, F. (2001) Systemic analgesia after block peripheral. Minerva Anestesiol. 67 (Suppl. 9): 195–199

Bingham, C. O. (2002) Development and clinical application of COX-2-selective inhibitors for the treatment of osteoarthritis and rheumatoid arthritis. Cleve. Clin. J. Med. 69 (Suppl. 1): SI5–SI12

Blain, H., Jouzeau, J. Y., Blain, A., Terlain, B., Trechot, P., Touchon, J., Netter, P., Jeandel, C. (2000) Non-steroidal antiinflammatory drugs with selectivity for cyclooxygenase-2 in alzheimer's disease. Rationale and perspectives. Presse Med. 29: 267–273

Block, S. H. (2002) Chronic sinusitis with rofecoxib. J. Allergy Clin. Immunol. 109: 373–374

Block, G. A., Lines, C. R. (2002) Combination of a GABAA alpha 5 inverse agonist and COX-2 inhibitor, NSAID, estrogen or vitamin E. Merck & Co., Inc., Rahway, NJ. US 6440967

Bombardier, C. (2002) An evidence-based evaluation of the gastrointestinal safety of coxibs. Am. J. Cardiol. 89: 3D–9D

Bombardier, C., Laine, L., Reicin, A., Shapiro, D., Burgos-Vargas, R., Davis, B., Day, R., Ferraz, M. B., Hawkey, C. J., Hochberg, M. C., Kvien, T. K., Schnitzer, T. J. (2000) Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR study group. N. Engl. J. Med. 343: 1520–1528

Bonnel, R. A., Villalba, M. L., Karwoski, C. B., Beitz, J. (2002) Aseptic meningitis associated with rofecoxib. Arch. Intern. Med. 162: 713–715

Boolbol, S. K., Dannenberg, A. J., Chadburn, A., Martucci, C., Guo, X. J., Ramonetti, J. T., Abreu-Goris, M., Newmark, H. L., Lipkin, M. L., DeCosse, J. J., Bertagnolli, M. M. (1996) Cyclooxygenase-2 overexpression and tumour formation are

blocked by sulindac in a murine model of familial adenomatous polyposis. Cancer Res. 56: 2556–2560
Bottner, F., Roedl, R., Wortler, K., Grethen, C., Winkelmann, W., Lindner, N. (2001) Cyclooxygenase-2 inhibitor for pain management in osteoid osteoma. Clin. Orthop. 393: 258–263
Brater, D. C. (1999) Effects of nonsteroidal antiinflammatory drugs on renal function: focus on cyclooxygenase-2-selective inhibition. Am. J. Med. 107: 65S–70S
Brater, D. C. (2002) Renal effects of cyclooxygyenase-2-selective inhibitors. J. Pain Symptom Manage. 23 (Suppl. 4): S15–S20
Brater, D. C., Harris, C., Redfern, J. S., Gertz, B. J. (2001) Renal effects of COX-2-selective inhibitors. Am. J. Nephrol. 21: 1–15
Brian, F. M. (2001) COX-2 inhibitors and cardiovascular risk: point and counterpoint. Cleve. Clin. J. Med. 68: 957–960
Brooks, P. M., Day, R. O. (2000) COX-2 inhibitors. Med. J. Aust. 173: 433–436
Brouwers, J. R. B. J., de Smet, P. A. G. M. (1994) Pharmacokinetic-pharmacodynamic drug interaction with nonsteroidal antiinflammatory drugs. Clin. Pharmacokinet. 27: 462–485
Brown, C. H. (2000) Effect of rofecoxib on the antihypertensive activity of lisinopril. Ann. Pharmacother. 34: 1486
Brown, J., Morrison, B. W., Christensen, S., Dunkley, V., Sandler, M., Turpin, M., Harmsen, B., Yuan, W., Lesneski, L., Seidenberg, B. (1999a) MK-0966 50 mg versus ibuprofen 400 mg in post-surgical dental pain. (abstract) Clin. Pharmacol. Ther. 65: 118, PI-4
Brown, J., Morrison, B. W., Bitner, M., Woolsey, C., Sandler, M., Dunkley, V., Kotey, P., Seidenberg, B. (1999b) The COX-2 specific inhibitor, MK-0966, is effective in the treatment of primary dysmenorrhoea. (abstract) Clin. Pharmacol. Ther. 65: 118, PI-5
Brune, K., Neubert, A. (2001) Pharmacokinetic and pharmacodynamic aspects of the ideal COX-2 inhibitor: a pharmacologist's perspective. Clin. Exp. Rheumatol. 19 (6 Suppl 25): S51–S57
Buchan, I. E., Bird, H. A. (1991) Drug interactions in arthritic patients. Ann. Rheum. Dis. 50: 680–681
Burleigh, M. E., Babaev, V. R., Oates, J. A., Harris, R. C., Gautam, S., Riendeau, D., Marnett, L. J., Morrow, J. D., Fazio, S., Linton, M. F. (2002) Cyclooxygenase-2 promotes early atherosclerotic lesion formation in LDL receptor-deficient mice. Circulation 105: 1816–1823
Cannon, G. W., Caldwell, J. R., Holt, P., McLean, B., Seidenberg, B., Bolognese, J., Ehrich, E., Mukhopadhyay, S., Daniels, B. (2000) Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Rofecoxib phase III protocol 035 study group. Arthritis Rheum. 43: 978–987
Carder, K. R., Weston, W. L. (2002) Rofecoxib-induced instant aquagenic wrinkling of the palms. Pediatr. Dermatol. 19:353–355
Caroli, A., Monica, F. (2001) Severe upper gastrointestinal bleeding during treatment with rofecoxib for osteoarthritis. Am. J. Gastroenterol. 96: 1663–1665
Catella, F., Nowak, J., Fitzgerald, G. A. (1986) Measurement of renal and non-renal eicosanoid synthesis. Am. J. Med. 81: 23–29
Catella-Lawson, F., Crofford, L. J. (2001) Cyclooxygenase inhibition and thrombogenicity. Am. J. Med. 110: 28S–32S
Catella-Lawson, F., McAdam, B., Morrison, B. W., Kapoor, S., Kujubu, D., Antes, L., Lasseter, K. C., Quan, H., Gertz, B. J., FitzGerald, G. A. (1999) Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J. Pharmacol. Exp. Ther. 289: 735–741
Catella-Lawson, F., Reilly, M. P., Kapoor, S. C., Cucchiara, A. J., DeMarco, S., Tournier, B., Vyas, S. N., FitzGerald, G. A. (2001) Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N. Engl. J. Med. 345: 1809–1817
Chan, C.-C., Boyce, S., Brideau, C., Charleson, S., Cromlish, W., Ethier, D., Evans, J., Ford-Hutchinson, A. W., Forrest, M. J., Gauthier, J. Y., Gordon, R., Gresser, M., Guay, J., Kargman, S., Kennedy, B., Leblanc, Y., Leger, S., Mancini, J., O'Neill, G. P., Ouellet, M., Patrick, D., Percival, M. D., Perrier, H., Prasit, P., Rodger, I., Tagari, P., Therien, M., Vickers, P., Visco, D., wang, Z., Webb, J., Wong, E., Xu, L.-J., Young, R. N., Zamboni, R., Riendeau, D. (1999) Rofecoxib [Vioxx, MK-0966; 4-(4′-methylsulfonylphenyl)-3-phenyl-2-(5H)-furanone]: a potent and orally active cyclooxygenase-2 inhibitor. Pharmacological and biochemical profiles. J. Pharmacol. Exp. Ther. 290: 551–560
Chang, D. J., Fricke, J. R., Bird, S. R., Bohidar, N. R., Dobbins, T. W., Geba, G. P. (2001) Rofecoxib versus codeine/acetaminophen in postoperative dental pain: a double-blind, randomized, placebo- and active comparator-controlled clinical trial. Clin. Ther. 23: 1446–1455
Chang, D. J., Desjardins, P. J., Chen, E., Polis, A. B., McAvoy, M., Mockoviak, S. H., Geba, G. P. (2002) Comparison of the analgesic efficacy of rofecoxib and enteric-coated diclofenac sodium in the treatment of postoperative dental pain: a randomized, placebo-controlled clinical trial. Clin. Ther. 24: 490–503
Chavez-Eng, C. M., Constanzer, M. L., Matuszewski, B. K. (2000) Determination of rofecoxib (MK-0966), a cyclooxygenase-2 inhibitor, in human plasma by high-performance liquid chromatography with tandem mass spectrometric detection. J. Chromatogr. B Biomed. Sci. Appl. 748: 31–39
Chavez-Eng, C. M., Constanzer, M. L., Matuszewski, B. K. (2002) High-performance liquid chromatographic-tandem mass spectrometric evaluation and determination of stable isotope labeled analogs of rofecoxib in human plasma samples from oral bioavailability studies. J. Chromatogr. B Biomed. Sci. Appl. 767: 117–129
Chen, F.-J., Patel, M. V. (2001) Clear oil-containing pharmaceutical compositions. Lipocine Inc., Salt Lake City, UT. US 6267985
Cheng, H. F., Wang, J. L., Zhang, M. Z., Miyazaki, Y., Ishikawa, I., McKanna, J. A., Harris, R. C. (1999) Angiotensin II stimulates renal cortical cyclooxygenase-2 expression. J. Clin. Invest. 103: 953–961
Chiolero, A., Wurzner, G., Burnier, M. (2000) Selective inhibitors of type 2 cyclooxygenase: less renal effects than the classical non-steroidal antiinflammatory agents. Nephrologie 21: 425–430
Cleland, L. G., James, M. J., Stamp, L. K., Penglis, P. S. (2001) COX-2 inhibition and thrombotic tendency: a need for surveillance. Med. J. Aust. 175: 214–217
Crofford, L. J. (2002) Specific cyclooxygenase-2 inhibitors: what have we learned since they came into widespread clinical use? Curr. Opin. Rheumatol. 14: 225–230
Cronstein, B. N. (2002) Cyclooxygenase-2-selective inhibitors: translating pharmacology into clinical utility. Cleve. Clin. J. Med. 69: SI13–SI19
Daniels, S., Morrison, B. W., Cantu, N., Sandler, M., Mccrary, L., Kotey, P., Seidenberg, B. (1999) Dose ranging trial of the effect of MK-0966 in primary dysmenorrhoea. (abstract) Clin. Pharmacol. Ther. 65: 118, PI-6
Day, R., Morrison, B., Luza, A., Castaneda, O., Strusberg, A., Nahir, M., Helgetveit, K. B., Kress, B., Daniels, B., Bolognese, J., Krupa, D., Seidenberg, B., Ehrich, E. (2000) A randomized

trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. Rofecoxib/ibuprofen comparator study group. Arch. Intern. Med. 160: 1781–1787

de La Serna Higuera, C., Rodriguez-Gomez, S. J., Martin Arribas, M. I., Martinez Moreno, J. (2002) Rofecoxib induced upper gastrontestinal bleeding. Med. Clin. (Barc) 118: 238

Depré, M., Ehrich, E. Van Hecken, A., De Lepeleire, I., Dallob, A., Wong, P., Porras, A., Gertz, B. J., De Schepper, P. J. (2000) Pharmacokinetics, COX-2 specificity, and tolerability of suprathera peutic doses of rofecoxib in humans. Eur. J. Clin. Pharmacol. 56: 167–174

Deray, G. (2001) Renal tolerance of selective inhibitors of cyclooxygenase type 2. Presse Med. 30: 1507–1512

Detora, L. M., Krupa, D., Bolognese, J., Sperling, R. S., Ehrich, E. W. (2001) Rofecoxib shows consistent efficacy in osteoarthritis clinical trials, regardless of specific patient demographic and disease factors. J. Rheumatol. 28: 2494–2503

DeWitt, D. L. (1991) Prostaglandin endoperoxide synthase: regulation of enzyme expression. Biochim. Biophys. Acta 111: 445–454

Dicker, A. P., Williams, T. L., Grant, D. S. (2001) Targeting angiogenic processes by combination rofecoxib and ionizing radiation. Am. J. Clin. Oncol. 24: 438–442

Dinchuk, J. E., Carr, B. D., Focht, R. J., Johnston, J. J., Jaffer, B. D., Covington, M. B., Contel, N. R., Eng, V. M., Collins, R. J., Czerniak, P. M., Gorry, S. A., Trzaskos, J. M. (1995) Renal abnormalities and an altered inflammatory response in mice lacking cyclooxygenase-2. Nature 378: 406–409

Eberhart, C. E., Coffey, R. Y., Radhica, A., Giardello, F. M., Ferrenbach, S., DuBois, R. N. (1994) Up regulation of cyclooxygenase-2 gene expression in human colorectal adenomas and adenocarcinom aas. Gastroenterology 107: 1183–1188

Ehrich, E. W., Dallob, A., De Lepeleire, I., Van Hecken, A., Riendeau, D., Yuan, W., Porras, A., Wittreich, J., Seibold, J. R., De Schepper, P., Mehlisch, D. R., Gertz, B. J. (1999a) Characterization of rofecoxib as a cyclooxygenase-2 isoform inhibitor and demonstration of analgesia in the dental pain model. Clin. Pharmacol. Ther. 65: 336–347

Ehrich, E. W., Schnitzer, T. J., McIlwain, H., Levy, R., Wolfe, F., Weisman, M., Zeng, Q., Morrison, B., Bolognese, J., Seidenberg, B., Gertz, B. J. (1999b) Effect of specific COX-2 inhibition in osteoarthritis of the knee: a 6 week double blind, placebo controlled pilot study of rofecoxib. Rofecoxib osteoarthritis pilot study group. J. Rheumatol. 26: 2438–2447

Ehrich, E. W., Davies, G. M., Watson, D. J., Bolognese, J. A., Seidenberg, B. C., Bellamy, N. (2000) Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. J. Rheumatol. 27: 2635–2641

Ehrich, E. W., Bolognese, J. A., Watson, D. J., Kong, S. X. (2001) Effect of rofecoxib therapy on measures of health-related quality of life in patients with osteoarthritis. Am. J. Manag. Care 7: 609–616

Enrique, E., Cistero-Bahima, A., San Miguel-Moncin, M. M., Alonso, R. (2000) Rofecoxib should be tried in NSAID hypersensitivity. Allergy 55: 1090

Faour, J., Coppari, M. A. (2001) Osmotic device within an osmotic device for drug delivery. Laboratories Phoenix U.S.A., Inc., USA. WO 2001051036, US 2002035357

FDA (1999a) NDA approvals for calender year 1999 of December, 1999. US FDA, Center for Drug Evaluation and Research, Rockville, MD. http://www.fda.gov/cder/rdmt/ndaaps99cy.htm (accessed 12 April 2003)

FDA (1999b) Listing of approved oncology drugs with approved indications. http://www.fda.gov/cder/cancer/druglistframe.htm, (accessed 24 April 2003)

FDA (2002a) Drug approvals for April, 2002. US FDA, Center for Drug Evaluation and Research, Rockville, MD. http://www.fda.gov/cder/da/da0402.htm (accessed 12 April 2003)

FDA (2002b) Information on Vioxx®. US FDA, Center for Drug Evaluation and Research, Rockville, MD. http://www.fda.gov/cder/foi/label/2002/21042s7lbl.pdf (accessed 11 April 2003)

Fendrick, A. M. (2002) Developing an economic rationale for the use of selective COX-2 inhibitors for patients at risk for NSAID gastropathy. Cleve. Clin. J. Med. 69 (Suppl. 1): SI59–SI64

Ferencik, M., Novak, M., Rovensky, J., Rybar, I. (2001) Alzheimer's disease, inflammation and non-steroidal antiinflammatory drugs. Bratisl. Lek. Listy. 102: 123–132

Ferguson, S., Hebert, R. L., Laneuville, O. (1999) NS-398 upregulates constitutive cyclooxygenase-2 expression in the M-1 cortical collecting duct cell line. J. Am. Soc. Physiol. 280: F43–F45

Ferreri, N. R., Shao-Jian, A., McGiff, J. (1999) Cyclooxygenase-2 expression and function in the medullary thick ascending limb. Am. J. Physiol. (Renal Physiol.) 277: F360–F368

FitzGerald, G. A., Patrono, C. (2001) The coxibs, selective inhibitors of cyclooxygenase-2. N. Engl. J. Med. 345: 433–442

FitzGerald, G. A., Cheng, Y., Austin, S. (2001) COX-2 inhibitors and the cardiovascular system. Clin. Exp. Rheumatol. 19 (Suppl. 25): S31–S36

Foral, P. A., Wilson, A. F., Nystrom, K. K. (2002) Gastrointestinal bleeds associated with rofecoxib. Pharmacotherapy 22: 384–386

Forgione, P., Wilson, P. D., Fallis, A. G. (2000) Magnesium mediated carbometallation of propargyl alcohols: direct routes to furans and furanones. Tetrahedron Lett. 41: 17–20

Fraley, M. E., Hartman, G. D., Hungate, R. W. (2002) Tyrosine kinase inhibitors. Merck & Co., Inc., Rahway, NJ. US 6420382

Frankish, H. (2002) Why do COX-2 inhibitors increase risk of cardiovascular events? Lancet 359: 1410

Freedman, G. M., Kreitzer, J. M., Badola, R. (2002) Rofecoxib-associated upper gastrointestinal bleed: a case report. Mt Sinai. J. Med. 69: 105–106

Freitas, J., Farricha, V., Nascimento, I., Borralho, P., Parames, A. (2002) Rofecoxib: a possible cause of acute colitis. J. Clin. Gastroenterol. 34: 451–453

Fricke, J., Morrison, B. W., Skip Fite, R. N., Sandler, M., Yuan, W., Howard, C., Seidenberg, B. (1999) MK-966 versus naproxen sodium 550 mg in post-surgical dental pain. (abstract) Clin. Pharmacol. Ther. 65: 119, PI-7

Fries, J. F. (1991) NSAID gastropathy: the second most deadly rheumatic disease? Epidemiology and risk appraisal. J. Rheumatol. 18 (Suppl. 28): 6–10

Frishman, W. H. (2002) Effects of nonsteroidal antiinflammatory drug therapy on blood pressure and peripheral edema. Am. J. Cardiol. 89: 18D–25D

Froelich, J. C., Wilson, T. W., Sweetman, B. J., Smigel, J. M., Nies, A. S., Carr, K., Watson, J. T., Oates, J. A. (1975) Urinary prostaglandins: identification and origin. J. Clin. Invest. 55: 763–770

Frost, P., Discafani-Marro, C. M. (2002) Method of treating or inhibiting colonic polyps and colorectal cancer. American Cyanamid Company, Madison, NJ US 6432979

Garner, S., Fidan, D., Frankish, R., Judd, M., Towheed, T., Wells, G., Tugwell, P. (2002) Rofecoxib for the treatment of rheumatoid arthritis (Cochrane Review). Cochrane Database Syst. Rev. 3: CD003685

Garnett, W. R. (2001) Clinical implications of drug interactions with coxibs. Pharmacotherapy 21: 1223–1232

Geba, G. P., Polis, A. B., Dixon, M. E., Dobbins, T. W., Rush, J. E., Weir, M. (2001) Comparative blood pressure effects of rofecoxib, celecoxib, and placebo in patients with osteoarthritis: a randomized controlled trial. (abstract) Ann. Rheum. Dis. 60 (Suppl. 1): 236, SAT0095

Geba, G. P., Weaver, A. L., Polis, A. B., Dixon, M. E., Schnitzer, T. J. (2002) Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: a randomized trial. JAMA 287: 64–71

Gertz, B. J., Krupa, D., Bolognese, J. A., Sperling, R. S., Reicin, A. (2002) A comparison of adverse renovascular experiences among osteoarthritis patients treated with rofecoxib and comparator non-selective non-steroidal antiinflammatory agents. Curr. Med. Res. Opin. 18: 82–91

Graham, G. G., Graham, R. I., Day, R. O. (2002) Comparative analgesia, cardiovascular and renal effects of celecoxib, rofecoxib and acetaminophen (paracetamol). Curr. Pharm. Des. 8: 1063–1075

Greenberg, H. E., Gottesdiener, K., Huntington, M., Wong, P., Larson, P., Wildonger, L., Gillen, L., Dorval, E., Waldman, S. A. (2000) A new cyclooxygenase-2 inhibitor, rofecoxib (VIOXX), did not alter the antiplatelet effects of low-dose aspirin in healthy volunteers. J. Clin. Pharmacol. 40: 1509–1515

Gretzer, B., Maricic, N., Respondek, M., Schuligoi, R., Peskar, B. M. (2001) Effects of specific inhibition of cyclo-oxygenase-1 and cyclo-oxygenase-2 in the rat stomach with normal mucosa and after acid challenge. Br. J. Pharmacol. 132: 1565–1573

Griswold, D. E., Adams, J. L. (1996) Constitutive cyclooxygenase (COX-1) and inducible cyclooxygenase (COX-2): rationale for selective inhibition and progress to date. Med. Res. Rev. 16: 181–206

Guo, J., Cho, C., Lam Liu, E., Choy, H., Wang, J., Leung Koo, M. (2002) Antiangiogenic effect of a highly selective cyclooxygenase-2 inhibitor on gastric ulcer healing in rats. Toxicol. Appl. Pharmacol. 183: 41

Halpin, R. A., Geer, L. A., Zhang, K. E., Marks, T. M., Dean, D. C., Jones, A. N., Melillo, D., Doss, G., Vyas, K. P. (2000) The absorption, distribution, metabolism and excretion of rofecoxib, a potent and selective cyclooxygenase-2 inhibitor, in rats and dogs. Drug Metab. Dispos. 28: 1244–1254

Halpin, R. A., Porras, A. G., Geer, L. A., Davis, M. R., Cui, D., Doss, G. A., Woolf, E., Musson, D., Matthews, C., Mazenko, R., Schwartz, J. I., Lasseter, K. C., Vyas, K. P., Baillie, T. A. (2002) The disposition and metabolism of rofecoxib, a potent and selective cyclooxygenase-2 inhibitor, in human subjects. Drug Metab. Dispos. 30: 684–693

Harris, R. C. (2002) Cyclooxygenase-2 inhibition and renal physiology. Am. J. Cardiol. 89: 10D–17D

Harris, R. C., McKanna, J. A., Akai, Y., Jacobson, H. R., Dubois, R. N., Breyer, M. D. (1994) Cyclooxygenase-2 is associated with the macula densa of kidney and increases with salt restriction. J. Clin. Invest. 94: 2504–2510

Hartman, R., Clausen, A., Mao, B., Abrahim, A., Crocker, L., Ge, Z. (2002) Investigation of the photostability of two COX-2 inhibitors, rofecoxib and etoricoxib, by HPLC using forced degradation. 224th ACS National Meeting, Boston, MA, US. (abstract) ANYL-074

Hawkey, C. J. (1999) COX-2 inhibitors. Lancet 353: 307–314

Hawkey, C. J. (2001) Gastrointestinal safety of COX-2 specific inhibitors. Gastroenterol. Clin. North Am. 30: 921–936

Hawkey, C. J., Laine, L., Simon, T., Beaulieu, A., Maldonado-Cocco, J., Acevedo, E., Shahane, A., Quan, H., Bolognese, J., Mortensen, E. (2000) Comparison of the effect of rofecoxib (a cyclooxygenase 2 inhibitor), ibuprofen, and placebo on the gastroduodenal mucosa of patients with osteoarthritis: a randomized, double-blind, placebo-controlled trial. The rofecoxib osteoarthritis endoscopy multinational study group. Arthritis Rheum. 43: 370–377

Hawkey, C. J., Jackson, L., Harper, S. E., Simon, T. J., Mortensen, E., Lines, C. R. (2001a) Review article: the gastrointestinal safety profile of rofecoxib, a highly selective inhibitor of cyclooxygenase-2, in humans. Aliment. Pharmacol. Ther. 15: 1–9

Hawkey, C. J., Laine, L., Harper, S. E., Quan, H. U., Bolognese, J. A., Mortensen, E. (2001b) Influence of risk factors on endoscopic and clinical ulcers in patients taking rofecoxib or ibuprofen in two randomized controlled trials. Aliment. Pharmacol. Ther. 15: 1593–1601

Hay, E., Derazon, H., Bukish, N., Katz, L., Kruglyakov, I., Armoni, M. (2002) Fatal hyperkalemia related to combined therapy with a COX-2 inhibitor, ACE inhibitor and potassium rich diet (1). J. Emerg. Med. 22: 349–352

Hillson, J. L., Furst, D. E. (2000) Rofecoxib. Expert. Opin. Pharmacother. 1: 1053–1066

Hinrichs, R., Ritzkowsky, A., Hunzelmann, N., Krieg, T., Scharffetter-Kochanek, K. (2001) Rofecoxib as an alternative in aspirin hypersensitivity. Allergy 56: 789

Hirsh, J. C., Midha, K. K., Hirsh, M., Lo, W.-Y. (2002) Multi-layered pharmaceutical composition for both intraoral and oral administration with polymeric coatings. Peirce Management, LLC, USA. Eur. Pat. Appl. EP 1260216

Ho, L. L., Brighton, T. (2002) Warfarin, antiplatelet drugs and their interactions. Aust. Prescriber 25: 81–85

Hochberg, M. C. (2001) What have we learned from the large outcomes trials of COX-2 selective inhibitors? The rheumatologist's perspective. Clin. Exp. Rheumatol. 19 (6 Suppl 25): S15–S22

Hocherl, K., Kammerl, M. C., Schumacher, K., Endemann, D., Grobecker, H. F., Kurtz, A. (2002a) Role of prostanoids in regulation of the renin-angiotensin-aldosterone system by salt intake. Am. J. Physiol. Renal Physiol. 283: F294–F301

Hocherl, K., Endemann, D., Kammerl, M. C., Grobecker, H. F., Kurtz, A. (2002b) Cyclo-oxygenase-2 inhibition increases blood pressure in rats. Br. J. Pharmacol. 136: 1117–1126

Huang, J. J., Taguchi, A., Hsu, H., Andriole, G. L., Kurz, A. (2001) Preoperative oral rofecoxib does not decrease postoperative pain or morphine consumption in patients after radical prostatectomy: a prospective, randomized, double-blinded, placebo-controlled trial. J. Clin. Anesth. 13: 94–97

Hunt, R. H., Bowen, B., Mortensen, E. R., Simon, T. J., James, C., Cagliola, A., Quan, H., Bolognese, J. A. (2000) A randomized trial measuring faecal blood loss after treatment with rofecoxib, ibuprofen, or placebo in healthy subjects. Am. J. Med. 109: 201–206

Hunt, R. H., Barkun, A. N., Baron, D., Bombardier, C., Bursey, F. R., Marshall, J. R., Morgan, D. G., Pare, P., Thomson, A. B., Whittaker, J. S. (2002) Recommendations for the appropriate use of antiinflammatory drugs in the era of the coxibs: defining the role of gastroprotective agents. Can. J. Gastroenterol. 16: 231–240

Husni, M. E., Solomon, D. H., Coblyn, J. S. (2002) Selective COX-2 inhibitors: towards defining their appropriate clinical role. J. Clin. Outcome Management 9: 265–268

Huster, D., Schubert, C., Berr, F., Mossner, J., Caca, K. (2002) Rofecoxib-induced cholestatic hepatitis: treatment with molecular adsorbent recycling system (MARS). J. Hepatol. 37: 413

Jackson, L. M., Hawkey, C. J. (2000) COX-2 selective nonsteroidal antiinflammatory drugs: do they really offer any advantages? Drugs 59: 1207–1216

Jaeschke, R., Gajewski, P., Brozek, J. (2002) Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. Circulation 106: e18

Jain, N. K., Patil, C. S., Kulkarni, S. K., Singh, A. (2002) Modulatory role of cyclooxygenase inhibitors in aging- and scopolamine or lipopolysaccharide-ind uced cognitive dysfunction in mice. Behav. Brain Res. 133: 369–376

Jamali, F., Sattari, S. (2000) High performance liquid chromatographic determination of cyclooxygenase II inhibitor rofecoxib in rat and human plasma. J. Pharm. Pharm. Sci. 3: 312–317

Jensen, B. L., Kurtz, A. (1997) Differential regulation of renal cyclooxygenase mRNA by dietary salt intake. Kidney Int. 52: 1242–1249

Kalgutkar, A. S., Zhao, Z. (2001) Discovery and design of selective cyclooxygenase-2 inhibitors as non-ulcerogenic, antiinflammatory drugs with potential utility as anti-cancer agents. Curr. Drug Targets 2: 79–106

Kammerl, M. C., Nsing, R. M., Schweda, F., Endemann, D., Stubanus, M., Kees, F., Lackner, K. J., Fischereder, M., Kramer, B. K. (2001a) Low sodium and furosemide-induced stimulation of the renin system in man is mediated by cyclooxygenase 2. Clin. Pharmacol. Ther. 70: 468–474

Kammerl, M. C., Nüsing, R. M., Richthammer, W., Kramer, B. K., Kurtz, A. (2001b) Inhibition of COX-2 counteracts the effects of diuretics in rats. Kidney Int. 60: 1684–1691

Kaplan-Machlis, B., Klostermeyer, B. S. (1999) The cyclooxygenase-2 inhibitors: safety and effectiveness. Ann. Pharmacother. 33: 979–988

Karali, T. T., Kontny, M. J., Le, T. T. (2002) Oral fast-melt dosage form of a cyclooxygenase-2 inhibitor. Pharmacia Corporation, USA. WO 2002015886

Kargman, S., Charlson, S., Cartwright, M., Frank, J., Riendeau, D., Mancini, J., Evans, J., O'Neill, G. (1996) Characterization of prostaglandin G/H synthase 1 and 2 in rat, dog, monkey, and human gastrointestinal tracts. Gastroenterology 111: 445–454

Kato, S., Takeuchi, K. (2002) Alteration of gastric ulcerogenic and healing responses in rats with adjuvant-ind uced arthritis. Jpn. J. Pharmacol. 89: 1–6

Kato, M., Nishida, S., Kitasato, H., Sakata, N., Kawai, S. (2001) Cyclooxygenase-1 and cyclooxygenase-2 selectivity of nonsteroidal antiinflammatory drugs: investigation using human peripheral monocytes. J. Pharm. Pharmacol. 53: 1679–1685

Katz, N. (2002) The impact of pain management on quality of life. J. Pain Symptom Manage. 24 (Suppl. 1): S38

Kaufman, W. E., Worley, P. F., Pegg, J., Bremer, M., Iskason, P. (1996) COX-2, a synaptically induced enzyme, is expressed by excitatory neurons at postsynaptic sites in rat cerebral cortex. Proc. Natl Acad. Sci. USA 93: 2317–2321

Kaur, C., Sarkar, R., Kanwar, A. J. (2001) Fixed drug eruption to rofecoxib with cross-reactivity to sulfonamides. Dermatology 203: 351

Kaur, B. S., Khamnehei, N., Iravani, M., Namburu, S. S., Lin, O., Triadafilopoulos, G. (2002) Rofecoxib inhibits cyclooxygenase 2 expression and activity and reduces cell proliferation in Barrett's oesophagus. Gastroenterology 123: 60–67

Kelkar, P. S., Butterfield, J. H., Teaford, H. G. (2001) Urticaria and angioedema from cyclooxygenase-2 inhibitors. J. Rheumatol. 28: 2553–2554

Kiang Y. H., Xu, W., Kaufman, M. J. (2003) Ab initio structure determination of rofecoxib from powder diffraction data using molecular packing analysis method and direct space method. Int. J. Pharm. 252: 213–223

Kirtikara, K., Swangkul, S., Ballou, L. R. (2001) The analysis of nonsteroidal antiinflammatory drug selectivity in prostaglandin G/H synthase (PGHS)-null cells. Inflamm. Res. 50: 327–332

Kitahara, M., Eitner, F., Ostendorf, T., Kunter, U., Janssen, U., Westenfeld, R., Matsui, K., Kerjaschki, D., Floege, J. (2002) Selective cyclooxygenase-2 inhibition impairs glomerular capillary healing in experimental glomerulonephritis. J. Am. Soc. Nephrol. 13: 1261–1270

Köhmhoff, M., Gröne, H.-J., Klein, T., Seyberth, H. W., Nsing, R. M. (1997) Localization of cyclooxygenase-1 and –2 in adult and foetal human kidney: implication for renal function. Am. J. Physiol. 272: F460–F468

Köhmhoff, M., Wang, J. L., Cheng, H. F., Langenbach, R., Mckanna, J. A., Harris, R. A., Breyer, M. D. (2000) Cyclooxygenase-2 selective inhibitors impair glomerulogenesis and renal cortical development. Kidney Int. 57: 414–422

Konstam, M. A., Weir, M. R. (2002) Current perspective on the cardiovascular effects of coxibs. Cleve. Clin. J. Med. 69 (Suppl. 1): SI47–SI52

Konstam, M. A., Weir, M. R., Reicin, A., Shapiro, D., Sperling, R. S., Barr, E., Gertz, B. J. (2001) Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. Circulation 104: 2280–2288

Krishna Reddy, K. V., Moses Babu, J., Dubey, P. K., Chandra Sekhar, B., Om Reddy, G., Vyas, K. (2002) Isolation and characterisation of process-related impurities in rofecoxib. J. Pharm. Biomed. Anal. 29: 355–360

Krymchantowski, A., Barbosa, J. (2002) Rizatriptan combined with rofecoxib vs. rizatriptan for the acute treatment of migraine: an open label pilot study. Cephalalgia 22: 309–312

Kumar, N. P., Wild, G., Ramasamy, K. A., Snape, J. (2002) Fatal haemorrhagic pulmonary oedema and associated angioedema after the ingestion of rofecoxib. Postgrad. Med. J. 78: 439–440

Laine, L. (2002) Gastrointestinal safety of coxibs and outcomes studies: what's the verdict? J. Pain Symptom Manage. 23 (Suppl. 4): S5–S10

Laine, L., Harper, S., Simon, T., Bath, R., Johanson, J., Schwartz, H., Stern, S., Quan, H., Bolognese, J. (1999) A randomized trial comparing the effect of rofecoxib, a cyclooxygenase 2-specific inhibitor, with that of ibuprofen on the gastroduodenal mucosa of patients with osteoarthritis. Rofecoxib osteoarthritis endoscopy study group. Gastroenterology 117: 776–783

Lanas, A. (2002) Clinical experience with cyclooxygenase-2 inhibitors. Rheumatology 41 (Suppl. 1): 16–22

Langman, M. J., Jensen, D. M., Watson, D. J., Harper, S. E., Zhao, P. L., Quan, H., Bolognese, J. A., Simon, T. J. (1999) Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 282: 1929–1933

Lanza, F. L., Rack, M. F., Simon, T. J., Quan, H., Bolognese, J. A., Hoover, M. E., Wilson, F. R., Harper, S. E. (1999) Specific inhibition of cyclooxygenase-2 with MK-0966 is associated with less gastroduodenal damage than either aspirin or ibuprofen. Aliment. Pharmacol. Ther. 13: 761–767

Laudanno, O. M., Cesolari, J. A., Esnarriaga, J., Rista, L., Piombo, G., Maglione, C., Aramberry, L., Sambrano, J., Godoy, A., Rocaspana, A. (2001) Gastrointestinal damage induced by celecoxib and rofecoxib in rats. Dig. Dis. Sci. 46: 779–784

Lew, J. I., Guo, Y., Kim, R. K., Vargish, L., Michelassi, F., Arenas, R. B. (2002) Reduction of intestinal neoplasia with adenomatous polyposis coli gene replacement and cox-2 inhibition is additive. J. Gastrointest. Surg. 6: 563–568

Lim, H., Paria, B. C., Das, S. K., Dinchuk, J. E., Langenbach, R., Trzaskos, J. M., Dey, S. K. (1997) Multiple female reproductive failures in cyclooxygenase 2 deficient mice. Cell 91: 197–208

Loewen, P. S. (2002) Review of the selective COX-2 inhibitors celecoxib and rofecoxib: focus on clinical aspects. Can. J. Emerg. Med. 4: 1–11

Lundmark, J., Gunnarsson, T., Bengtsson, F. (2002) A possible interaction between lithium and rofecoxib. Br. J. Clin. Pharmacol. 53: 403–404

Luong, C., Miller A., Barnett, J., Chow, J., Ramasha, C., Browner M. F. (1996) The structure of human cyclooxygenase-2; conservation and flexibility of the NSAID binding site. Nat. Struct. Biol. 3: 927–933

Mahadevan, U., Loftus, E. V., Jr. Tremaine, W. J., Sandborn, W. J. (2002) Safety of selective cyclooxygenase-2 inhibitors in inflammatory bowel disease. Am. J. Gastroenterol. 97: 910–914

Malmstrom, K., Daniels, S., Kotey, P., Seidenberg, B. C., Desjardins, P. J. (1999) Comparison of rofecoxib and celecoxib, two cyclooxygenase-2 inhibitors, in postoperative dental pain: a randomized, placebo- and active-comparator-controlled clinical trial. Clin. Ther. 21: 1653–1663

Malmstrom, K., Fricke, J. R., Kotey, P., Kress, B., Morrison, B. (2002) A comparison of rofecoxib versus celecoxib in treating pain after dental surgery: a single-center, randomized, double-blind, placebo- and active-comparator- controlled, parallel-group, single-dose study using the dental impaction pain model. Clin. Ther. 24: 1549–1560

Mao, B., Abrahim, A., Ge, Z., Ellison, D. K., Hartman, R., Prabhu, S. V., Reamer, R. A., Wyvratt, J. (2002) Examination of rofecoxib solution decomposition under alkaline and photolytic stress conditions. J. Pharm. Biomed. Anal. 28: 1101–1113

Marshall, J. K., Pellissier, J. M., Attard, C. L., Kong, S. X., Marentette, M. A. (2001) Incremental cost-effectiveness analysis comparing rofecoxib with nonselective NSAIDs in osteoarthritis: Ontario Ministry of Health perspective. Pharmacoeconomics 19: 1039–1049

Martin-Garcia, C., Hinojosa, M., Berges, P., Camacho, E., Garcia-Rodriguez, R., Alfaya, T., Iscar, A. (2002) Safety of a cyclooxygenase-2 inhibitor in patients with aspirin-sensitive asthma. Chest 121: 1812–1817

Matheson, A. J., Figgitt, D. P. (2001) Rofecoxib: a review of its use in the management of osteoarthritis, acute pain and rheumatoid arthritis. Drugs 61: 833–865

Matthews, C. Z., Woolf, E. J., Matuszewski, B. K. (2002) Improved procedure for the determination of rofecoxib in human plasma involving 96-well solid-phase extraction and fluorescence detection. J. Chromatogr. A 949: 83–89

Mayan, H., Gurevitz, O., Farfel, Z. (2002) Successful treatment by cyclooxyenase-2 inhibitor of refractory hypokalemia in a patient with Gitelman's syndrome. Clin. Nephrol. 58: 73–76

McGeer, P. L., McGeer, E. G. (1995) The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. Brain Res. Rev. 21: 195–218

McMurray, R. W., Hardy, K. J. (2002) Cox-2 inhibitors: today and tomorrow. Am. J. Med. Sci. 323: 181–189

Meade, E. A., Smith, W. L., DeWitt, D. L. (1993) Differential inhibition of prostaglandin endoperoxide synthase (cyclooxygenase) isozymes by aspirin and other non-steroidal antiinflammatory drugs. J. Biol. Chem. 268: 6610–6614

Mehlisch, D. R., Mills, S., Sandler, M., Yuan, W., Dury, W., Ehrich, E., Seidenberg, B., Morrison, B. (1998) Ex vivo assay of COX-2 inhibition predicts analgesic efficacy in post-surgical dental pain with MK-966. (abstract) Clin. Pharmacol. Ther. 63: 139, PI-8

Merck & Co., Inc. (1998) VIOXX (rofecoxib tablets and oral suspension). Merck & Co., Inc., Whitehouse Station, New Jersey, USA

Meyer, R. (2002) Rofecoxib reduces perioperative morphine consumption for abdominal hysterectomy and laparoscopic gastric banding. Anaesth. Intensive Care 30: 389–390

Miralpeix, M., Camacho, M., Lopez-Belmonte, J., Canalias, F., Beleta, J., Palacios, J. M., Vila, L. (1997) Selective induction of cyclooxygenase-2 activity in the permanent human endothelial cell line HUV-EC-C: biochemical and pharmacological characterization. Br. J. Pharmacol. 121: 171–180

Mitchell, J. A., Akaraserennont, P., Thiemermann, C., Flower, R. J., Vane, J. R. (1994) Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. Proc. Natl Acad. Sci. USA 90: 11693–11697

Mizuno, H., Sakamoto, C., Matsuda, K., Wada, K., Hahida, T., Noguabi, H., Akamatsu, T., Kasuga, M. (1997) Induction of cyclooxygenase 2 in gastric mucosal lesions and its inhibition by specific antagonist delays healing in mice. Gastroenterology 112: 387–397

Moore, P. A., Hersh, E. V. (2001) Celecoxib and rofecoxib. The role of COX-2 inhibitors in dental practice. J. Am. Dent. Assoc. 132: 451–456

Morrison, B. W., Christensen, S., Yuan, W., Brown, J., Amlani, S., Seidenberg, B. (1999a) Analgesic efficacy of the cyclooxygenase-2-specific inhibitor rofecoxib in post-dental surgery pain: a randomized, controlled trial. Clin. Ther. 21: 943–953

Morrison, B. W., Daniels, S. E., Kotey, P., Cantu, N., Seidenberg, B. (1999b) Rofecoxib, a specific cyclooxygenase-2 inhibitor, in primary dysmenorrhoea: a randomized controlled trial. Obstet. Gynecol. 94: 504–508

Morrison, B. W., Fricke, J., Brown, J., Yuan, W., Kotey, P., Mehlisch, D. (2000) The optimal analgesic dose of rofecoxib: Overview of six randomized controlled trials. J. Am. Dent. Assoc. 131: 1729–1737

Mukherjee, D. (2002) Selective cyclooxygenase-2 (COX-2) inhibitors and potential risk of cardiovascular events. Biochem. Pharmacol. 63: 817–821

Mukherjee, D., Nissen, S. E., Topol, E. J. (2001) Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 286: 954–959

Murpani, D., Malik, R. (2002) Process for the preparation of a fast dissolving dosage form. Ranbaxy Laboratories Ltd., India. WO 2002047607

Naesdal, J., Wilson, I. (2001) Gastro-duodenal protection in an era of cyclo-oxygenase-2-selective nonsteroidal antiinflammatory drugs. Eur. J. Gastroenterol. Hepatol. 13: 1401–1406

Nettis, E., Di, P. R., Ferrannini, A., Tursi, A. (2002) Tolerability of rofecoxib in patients with cutaneous adverse reactions to nonsteroidal antiinflammatory drugs. Ann. Allergy Asthma Immunol. 88: 331–334

Niccoli, L., Bellino, S., Cantini, F. (2002) Renal tolerability of three commonly employed non-steroidal antiinflammatory drugs in elderly patients with osteoarthritis. Clin. Exp. Rheumatol. 20: 201–207

Noble, S. L., King, D. S., Olutade, J. I. (2000) Cyclooxygenase-2 enzyme inhibitors: place in therapy. Am. Fam. Physician. 61: 3669–3676

Noroian, G., Clive, D. (2002) Cyclo-oxygenase-2 inhibitors and the kidney: a case for caution. Drug Saf. 25: 165–172

Ofran, Y., Bursztyn, M., Ackerman, Z. (2001) Rofecoxib-induced renal dysfunction in a patient with compensated cirrhosis and heart failure. Am. J. Gastroenterol. 96: 1941

Olszynski, W. P., Sylwestrowicz, T. A., Pylypchuk, G. B., Regler, L. D. (2002) Coxibs in clinical practice: towards a Saskatchewan consensus. In: RxFiles; the RxFiles academic program. Saskatoon City Hospital, Saskatoon, SK, Canada available at www.sdh.sk.ca/rxfiles/acrobat/coxibs2002-consensus-header.pdf (accessed 11 April 2003)

Oshima, M., Murai, N., Kargman, S., Arguello, M., Luk, P., Kwong, E., Taketo, M. M., Evans, J. F. (2001) Chemoprevention of intestinal polyposis in the Apcdelta716 mouse by rofecoxib, a specific cyclooxygenase-2 inhibitor. Cancer Res. 61: 1733–1740

Osterhaus, J. T., Burke, T. A., May, C., Wentworth, C., Whelton, A., Bristol, S. (2002) Physician-reported management of edema and destabilized blood pressure in cyclooxygenase-2-specific inhibitor users with osteoarthritis and treated hypertension. Clin. Ther. 24: 969–989

Ouellet, M., Riendeau, D., Percival, M. D. (2001) A high level of cyclooxygenase-2 inhibitor selectivity is associated with a reduced interference of platelet cyclooxygenase-1 inactivation by aspirin. Proc. Natl Acad. Sci. USA 98: 14583–14588

Pacor, M. L., Di Lorenzo, G., Biasi, D., Barbagallo, M., Corrocher, R. (2002) Safety of rofecoxib in subjects with a history of adverse cutaneous reactions to aspirin and/or nonsteroidal antiinflammatory drugs. Clin. Exp. Allergy 32: 397–400

Pall, M., Friden, B. E., Brannstrom, M. (2001) Induction of delayed follicular rupture in the human by the selective COX-2 inhibitor rofecoxib: a randomized double-blind study. Hum. Reprod. 16: 1323–1328

Palmer, R. H. (2001) Discussion on rofecoxib, a COX-2 inhibitor, does not inhibit human gastric mucosal prostaglandin production. Gastroenterology 121: 1262–1263

Pascucci, R. A. (1999) COX-2-specific inhibition: implications for clinical practice. J. Am. Osteopath. Assoc. 99 (Suppl. 11): S18–S22

Patel, M. V., Chen, F.-J. (2001) Triglyceride-free compositions and methods for improved delivery of hydrophobic therapeutic agents. Lipocine, Inc., Salt Lale City, UT. US 6294192

Patti, R., Gumired, K., Reddanna, P., Sutton, L. N., Phillips, P. C., Reddy, C. D. (2002) Overexpression of cyclooxygenase-2 (COX-2) in human primitive neuroectodermal tumors: effect of celecoxib and rofecoxib. Cancer Lett. 180: 13–21

Pedros, C., Cereza, G., Laporte, J. R. (2002) First spontaneous reports of adverse reactions to the new selective COX-2 nonsteroidal antiinflammatory drugs. Med. Clin. (Barc.) 118: 415–417

Perazella, M. A., Tray, K. (2001) Selective cyclooxygenase-2 inhibitors: a pattern of nephrotoxicity similar to traditional nonsteroidal antiinflammatory drugs. Am. J. Med. 111: 64–67

Peres, M. F., Silberstein, S. D. (2002) Hemicrania continua responds to cyclooxygenase-2 inhibitors. Headache 42: 530–531

Peres, M. F., Zukerman, E. (2000) Hemicrania continua responsive to rofecoxib. Cephalalgia 20: 130–131

Peretz, A. (2001) COX-2 inhibitor non-steroidal antiinflammatory drugs, myth or reality? Rev. Med. Brux. 22: A377–A380

Peura, D. A. (2002) Gastrointestinal safety and tolerability of nonselective nonsteroidal antiinflammatory agents and cyclooxygenase-2-selective inhibitors. Cleve. Clin. J. Med. 69: (Suppl. 1): SI31–SI39

Pickering, A. E., Bridge, H. S., Nolan, J., Stoddart, P. A. (2002) Double-blind, placebo-controlled analgesic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children. Br. J. Anaesth. 88: 72–77

Picot, D., Loll, P. J., Garavito, R. M. (1994) The X-ray crystal structure of the membrane protein prostaglandin H2 synthase-1. Nature 367: 243–249

Quiralte, J., Saenz de San Pedro, B., Florido, J. J. (2002) Safety of selective cyclooxygenase-2 inhibitor rofecoxib in patients with NSAID-induced cutaneous reactions. Ann. Allergy Asthma Immunol. 89: 63–66

Radhakrishna, T., Sreenivas Rao, D., Om Reddy, G. (2001) LC determination of rofecoxib in bulk and pharmaceutical formulations. J. Pharm. Biomed. Anal. 26: 617–628

Radi, A. (2002) Adsorptive stripping square-wave voltammetric behavior of rofecoxib. Microchemical J. 72: 35–41

Rajadhyaksha, V. D., Dahanukar, S. A. (2001) Rofecoxib: a new selective COX-2 inhibitor. J. Postgrad. Med. 47: 77–78

Reddy, B. S., Rao, C. V. (2002) Novel approaches for colon cancer prevention by cyclooxygenase-2 inhibitors. J. Environ. Pathol. Toxicol. Oncol. 21: 155–164

Reddy, M. N., Murthy, T. K., Shanta Kumar, S. M. (2002) UV and visible spectrophotometeric methods for the determination of rofecoxib. Indian Drugs 39: 39–40

Rehman, Q., Sack, K. E. (1999) When to try COX-2-specific inhibitors. Safer than standard NSAIDs in some situations. Postgrad. Med. 106: 95–106

Reicin, A., Brown, J., Jove, M., deAndrade, J. R., Bourne, M., Krupa, D., Walters, D., Seidenberg, B. (2001) Efficacy of single-dose and multidose rofecoxib in the treatment of postorthopedic surgery pain. Am. J. Orthop. 30: 40–48

Reicin, A. S., Shapiro, D., Sperling, R. S., Barr, E., Yu, Q. (2002) Comparison of cardiovascular thrombotic events in patients with osteoarthritis treated with rofecoxib versus nonselective nonsteroidal antiinflammatory drugs (ibuprofen, diclofenac, and nabumetone). Am. J. Cardiol. 89: 204–209

Reinalter, S. C., Jeck, N., Brochhausen, C., Watzer, B., Nusing, R. M., Seyberth, H. W., Komhoff, M. (2002) Role of cyclooxygenase-2 in hyperprostaglandin E syndrome/antenatal Bartter syndrome. Kidney Int. 62: 253–260

Reitblat, T., Zamir, D., Estis, L., Priluk, R., Drogenikov, T., Viskoper, J. R. (2002) The different patterns of blood pressure elevation by rofecoxib and nabumetone. J. Hum. Hypertens. 16: 431–434

Rekha, K. S., Vyas, K., Raju, C. M. H., Chandrashekhar, B., Reddy, G. O. (2000) Vioxx, a COX-II inhibitor. Acta Crystallogr. Sect. C Cryst. Struct. Commun. 56: e68

Reuben, S. S., Connelly, N. R. (2000) Postoperative analgesic effects of celecoxib or rofecoxib after spinal fusion surgery. Anesth. Analg. 91: 1221–1225

Reuben, S. S., Bhopatkar, S., Maciolek, H., Joshi, W., Sklar, J. (2002a) The preemptive analgesic effect of rofecoxib after ambulatory arthroscopic knee surgery. Anesth. Analg. 94: 55–59

Reuben, S. S., Fingeroth, R., Krushell, R., Maciolek, H. (2002b) Evaluation of the safety and efficacy of the perioperative administration of rofecoxib for total knee arthroplasty. J. Arthroplasty 17: 26–31

Ristimaki, A., Honkanen, H., Jaukala, H., Sepponen, P., Harkonen, M. (1997) Expression of cyclooxygenase-2 in human gastric carcinoma. Cancer Res. 57: 1276–1280

Robertson, E. P. (1998) Dominance of cyclooxygenase-2 in the regulation of pancreatic islet prostaglandin synthesis. Diabetes 47: 1379–1383

Rocha, J. L., Fernandez-Alonso, J. (2001) Acute tubulointerstitial nephritis associated with the selective COX-2 enzyme inhibitor, rofecoxib. Lancet 357: 1946–1947

Rodrigues, A. D., Halpin, R. A., Geer, L. A., Cui, D., Woolf, E. J., Matthews, C. Z., Gottesdiener, K. M., Larson, P. J., Lasseter, K. C., Agrawal, N. G. B. (2003) Absorption, metabolism, and excretion of etoricoxib, a potent and selective cyclooxygenase-2 inhibitor, in healthy male volunteers. Drug Metab. Dispos. 31: 224–232

Roth, S. H. (1986) Nonsteroidal antiinflammatory drug gastropathy: we started it – can we stop it? Arch. Intern. Med. 146: 1075–1076

Saag, K., D. van der Heijde, D., Fisher, C., Samara, A., DeTora, L., Bolognese, J., Sperling, R., Daniels, B. (2000) Rofecoxib, a new cyclooxygenase 2 inhibitor, shows sustained efficacy, comparable with other nonsteroidal antiinflammatory drugs: a 6-week and a 1-year trial in patients with osteoarthritis. Osteoarthritis studies group. Arch. Fam. Med. 9: 1124–1134

Sanchez Borges, M., Capriles-Hulett, A., Caballero-Fonseca, F., Perez, C. R. (2001) Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. Ann. Allergy Asthma Immunol. 87: 201–204

Sandrini, M., Vitale, G., Pini, L. A. (2002) Effect of rofecoxib on nociception and the serotonin system in the rat brain. Inflamm. Res. 51: 154–159

Scheen, A. J. (2000) Pharma-clinics. The drug of the month. Rofecoxib (Vioxx). Rev. Med. Liege. 55: 751–753

Scheiman, J. M. (2002) Outcomes studies of the gastrointestinal safety of cyclooxygenase-2 inhibitors. Cleve. Clin. J. Med. 69 (Suppl. 1): SI40–SI46

Schnitzer, T. J. (2001) Osteoarthritis management: the role of cyclooxygenase-2-selective inhibitors. Clin. Ther. 23: 313–326

Schnitzer, T. J., Hochberg, M. C. (2002) COX-2-selective inhibitors in the treatment of arthritis. Cleve. Clin. J. Med. 69 (Suppl. 1): SI20–SI30

Schnitzer, T. J., Truitt, K., Fleischmann, R., Dalgin, P., Block, J., Zeng, Q., Bolognese, J., Seidenberg, B., Ehrich, E. W. (1999) The safety profile, tolerability, and effective dose range of rofecoxib in the treatment of rheumatoid arthritis. Phase II rofecoxib rheumatoid arthritis study group. Clin. Ther. 21: 1688–1702

Schoors, D. (2002) A comparison of the renal and cardiovascular safety of celecoxib and rofecoxib. Clin. Ther. 24: 468–469

Schwartz, J., Hsieh, P., Ebel, D., Hunt, T., Gertz, B. (1997) Influence of selective cyclooxygenase-2 inhibitor, MK-0966, on ethinylestradiol (EE) and norethindrone (NET) serum concentrations. (abstract) Eur. J. Clin. Pharmacol. 52 (Suppl.): A113

Schwartz, J. I., Chan, C. C., Mukhopadhyay, S., McBride, K. J., Jones, T. M., Adcock, S., Moritz, C., Hedges, J., Grasing, K., Dobratz, D., Cohen, R. A., Davidson, M. H., Bachmann, K. A., Gertz, B. J. (1999) Cyclooxygenase-2 inhibition by rofecoxib reverses naturally occurring fever in humans. Clin. Pharmacol. Ther. 65: 653–660

Schwartz, J., Zhao, P., Gertz, B., Gumbs, C., Ebel, D., Lasseter, K., Porras, A. (2000a) Pharmacokinetics of rofecoxib in mild to moderate hepatic insufficiency (HI). (abstract) Clin. Pharmacol. Ther. 67: 137, PII-90

Schwartz, J. I., Bugianesi, K. J., Ebel, D. L., De Smet, M., Haesen, R., Larson, P. J., Ko, A., Verbesselt, R., Hunt, T. L., Lins, R., Lens, S., Porras, A. G., Dieck, J., Keymeulen, B., Gertz, B. J. (2000b) The effect of rofecoxib on the pharmacodynamics and pharmcokinetics of warfarin. Clin. Pharmacol. Ther. 68: 626–636

Schwartz, J. I., Agrawal, N. G., Wong, P. H., Bachmann, K. A., Porras, A. G., Miller, J. L., Ebel, D. L., Sack, M. R., Holmes, G. B., Redfern, J. S., Gertz, B. J. (2001a) Lack of pharmacokinetic interaction between rofecoxib and methotrexate in rheumatoid arthritis patients. J. Clin. Pharmacol. 41: 1120–1130

Schwartz, J. I., De Smet, M., Larson, P. J., Verbesselt, R., Ebel, D. L., Lins, R., Lens, S., Porras, A. G., Gertz, B. J. (2001b) Effect of rofecoxib on the pharmacokinetics of digoxin in healthy volunteers. J. Clin. Pharmacol. 41: 107–112

Schwartz, J. I., Wong, P. H., Porras, A. G., Ebel, D. L., Hunt, T. R., Gertz, B. J. (2002) Effect of rofecoxib on the pharmacokinetics of chronically administered oral contraceptives in healthy female volunteers. J. Clin. Pharmacol. 42: 215–221

Schwartz, J. I., Mukhopadhyay, S., Porras, A. G., Viswanathan-Aiyer, K. J., Adcock, S., Ebel, D. L., Gertz, B. J. (2003) Effect of rofecoxib on prednisolone and prednisone pharmacokinetics in healthy subjects. J. Clin. Pharmacol. 43: 187–192

Scott, L. J., Lamb, H. M. (1999) Rofecoxib. Drugs 58: 499–505

Searle & Co., Inc. (1999) US FDA draft label for Celebrex (Celecoxib capsules). Available at www.fda.gov/cder/foi/label/1998/20998lbl.pdf (accessed 10 April 2003)

Searle Ltd (2002) Information on clinical pharmacology of Valdecoxib. Available at www.rxlist.com/cgi/generic/bextra_cp.htm (accessed 12 April 2003)

Seibold, J. R., Spector, R. (2001) NSAIDs and COX-2 inhibitors: selective vs standard use. Med. Crossfire 3: 49–53

Selzer, T. (2002) Dermal therapeutic system containing nonsteroidal antiphlogistics with selective COX-2 inhibition. LTS Lohmann Therapie-Systeme Ag, Germany DE 10032132

Shen, F., Bai, A. P., Guo, Z. R., Cheng, G. F. (2002) Inhibitory effect of 3,4-diaryl-3-pyrrolin-2-one derivatives on cyclooxygenase 1 and 2 in murine peritoneal macrophages. Acta. Pharmacol. Sin. 23: 762–768

Sigthorsson, G., Crane, R., Simon, T., Hoover, M., Quan, H., Bolognese, J. A., Bjarnason, I. (2000) COX-2 inhibition with rofecoxib does not increase intestinal permeability in healthy subjects: a double blind crossover study comparing rofecoxib with placebo and indomethacin. Gut 47: 527–532

Simitchieva, K., Reines, S. A., McKinney, E., Sandquiest, E. J., Khannna, D. K., Hargreaves, R. (2002) Method of treating migraines and pharmaceutical compositions. Merck & Co., Inc., Rahway, NJ. US 6384034

Simon, L. S. (2001) COX-2 inhibitors. Are they nonsteroidal antiinflammatory drugs with a better safety profile? Gastroenterol. Clin. North Am. 30: 1011–1025

Sinatra, R. (2002) Role of cox-2 inhibitors in the evolution of acute pain management. J. Pain Symptom Manage. 24 (Suppl. 1): S18

Singh, A., Jain, R. (2001) Antiinflammatory and analgesic composition containing COX-2 inhibitors for topical and transdermal uses. Panacea Biotec Ltd, India. WO 2001052897

Singh, B., Singh, A., Ahuja, N. (2003) Studies on dissolution enhancement of rofecoxib using water-soluble carriers. In: National seminar on pharmaceutics in the light of drug delivery challenges. Chandigarh, India, 14–15 March (abstract) P-11

Singh, G., Ramey, D. R., Morfield, D., Shi, H., Hatoum, H. T., Fries, J. F. (1996) Gastrointestinal tract complications of nonsteroidal antiinflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. Arch. Intern. Med. 156: 1530–1536

Singla, A. K., Chawla, M., Singh, A. (2000) Nimesulide: some pharmaceutical and pharmacological aspects – an update. J. Pharm. Pharmacol. 52: 467–486

Slaughter, R. L., Edwards, D. J. (1995) Recent advances: the cytochrome P450 enzymes. Ann. Pharmacother. 29: 619–624

Smith, W. L., DeWitt, D. L. (1996) Prostaglandin endoperoxide H synthases-1 and -2. Adv. Immunol. 62: 167–215

Smith, W. L., Garovito, D. E., DeWitt, D. L. (1996) Prostaglandin endoperoxide H synthases (cyclooxygenase)-1 and -2. J. Biol. Chem. 271: 33157–33160

Steinfeld, S., Poriau, S. (2001) Patient and physician satisfaction with rofecoxib in osteoarthritis: results of the EVA (experience with VIOXX in arthritis) survey. Curr. Med. Res. Opin. 17: 81–87

Steinfeld, S., Bjorke, P. A. (2002) Results from a patient survey to assess gastrointestinal burden of non-steroidal anti-inflammatory drug therapy contrasted with a review of data from EVA to determine satisfaction with rofecoxib. Rheumatology 41 (Suppl. 1): 23–27

Stevenson, D. D., Simon, R. A. (2001) Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. J. Allergy Clin. Immunol. 108: 47–51

Straub, J., Bernstein, H., Chickering, III, Donald, E., Khattak, S., Randall, G. (2002) Porous drug matrices and methods of manufacture thereof. Acusphere, Inc., Cambridge, MA. US 6395300

Sundy, J. S. (2001) COX-2 inhibitors in rheumatoid arthritis. Curr. Rheumatol. Rep. 3: 86–91

Supersaxo, A. W., Weder, M. A., Weder, H. G. (2002) Microemulsion preconcentrates as pharmaceutical formulations for anti-inflammatory compounds with low solubility. Vesifact Ag, Switzerland. Eur. Pat. Appl., EP 1249231

Swan, S. K., Rudy, D. W., Lasseter, K. C., Ryan, C. F., Buechel, K. L., Lambrecht, L. J., Pinto, M. B., Dilzer, S. C., Obrda, O., Sundblad, K. J., Gumbs, C. P., Ebel, D. L., Quan, H., Larson, P. J., Schwartz, J. I., Musliner, T. A., Gertz, B. J., Brater, D. C., Yao, S. L. (2000) Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet. A randomized, controlled trial. Ann. Intern. Med. 133: 1–9

Szczeklik, A., Nizankowska, E., Bochenek, G., Nagraba, K., Mejza, F., Swierczynska, M. (2001) Safety of a specific COX-2 inhibitor in aspirin-induced asthma. Clin. Exp. Allergy 31: 219–225

Tanaka, A., Araki, H., Komoike, Y., Hase, S., Takeuchi, K. (2001) Inhibition of both COX-1 and COX-2 is required for development of gastric damage in response to nonsteroidal antiinflammatory drugs. J. Physiol. Paris 95: 21–27

Tanaka, A., Araki, H., Hase, S., Komoike, Y., Takeuchi, K. (2002a) Up-regulation of COX-2 by inhibition of COX-1 in the rat: a key to NSAID-induced gastric injury. Aliment. Pharmacol. Ther. 16 (Suppl. 2): 90–101

Tanaka, A., Hase, S., Miyazawa, T., Takeuchi, K. (2002b) Up-regulation of cyclooxygenase-2 by inhibition of cyclooxygenase-1: a key to nonsteroidal antiinflammatory drug-induced intestinal damage. J. Pharmacol. Exp. Ther. 300: 754–761

Thérien, M., Gauthier, J. Y., Leblanc, Y., Léger. S., Perrier, H., Prasit, P., Wang, Z. (2001) Synthesis of rofecoxib, (MK 0966, Vioxx 4-(4′-methylsulphonylphenyl)-3-phenyl-2(5 H)-furanone), a selective and orally active inhibitor of cyclooxygenase-2. Synthesis 12: 1778–1779

Truitt, K. E., Sperling, R. S., Ettinger, W. H., Greenwald, M., DeTora, L., Zeng, Q. Bolognese, J., Ehrich, E. (2001) A multicenter, randomized, controlled trial to evaluate the safety profile, tolerability, and efficacy of rofecoxib in advanced elderly patients with osteoarthritis. Aging (Milano) 13: 112–121

Vadas, P., Stefanski, E., Wloch, M., Grouix, B., van den Bosch, H., Kennedy, B. (1996) Secretory non-pancreatic phospholipase A2 and cyclooxygenase-2 expression by tracheobronchial smooth muscle cells. Eur. J. Biochem. 235: 557–563

Van Hecken, A., Schwartz, J. I., Depre, M., De Lepeleire, I., Dallob, A., Tanaka, W., Wynants, K., Buntinx, A., Arnout, J., Wong, P. H., Ebel, D. L., Gertz, B. J., De Schepper, P. J. (2000) Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. J. Clin. Pharmacol. 40: 1109–1120

Vane, J. R. (1971) Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat. New Biol. 231: 232–235

Vane, J. R., Botting, R. M. (1995) New insights into the mode of action of antiinflammatory drugs. Inflamm. Res. 44: 1–10

Verma, S., Raj, S. R., Shewchuk, L., Mather, K. J., Anderson, T. J. (2001) Cyclooxygenase-2 blockade does not impair endothelial vasodilator function in healthy volunteers: randomized evaluation of rofecoxib versus naproxen on endothelium-dependent vasodilatation. Circulation 104: 2879–2882

Wahba, A. L., Soper, C. (2001) Acute, anuric renal failure associated with two doses of a cyclooxygenase-2 inhibitor. Nephron 89: 239

Watson, D. J., Harper, S. E., Zhao, P. L., Quan, H., Bolognese, J. A., Simon, T. J. (2000) Gastrointestinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with nonselective COX-1 and COX-2 inhibitors in osteoarthritis. Arch. Intern. Med. 160: 2998–3003

Watson, D. J., Harper, S. E., Zhao, P. L., Bolognese, J. A., Simon, T. J. (2001) Gastrointestinal medications and procedures in osteoarthritis patients treated with rofecoxib compared with nonselective NSAIDs. Med. Gen. Med. 3: 6

Weaver, A. L. (2001) Rofecoxib: clinical pharmacology and clinical experience. Clin. Ther. 23: 1323–1338

Weaver, J., Bonnel, R. A., Karwoski, C. B., Brinker, A. D., Beitz, J. (2001) GI events leading to death in association with celecoxib and rofecoxib. Am. J. Gastroenterol. 96: 3449–3450

Werner, U., Werner, D., Mundkowski, R., Gillich, M., Brune, K. (2001) Selective and rapid liquid chromatography-mass spectrometry method for the quantification of rofecoxib in pharmacokinetic studies with humans. J. Chromatogr. B Biomed. Sci. Appl. 760: 83–90

Whelton, A. (2001) Cyclooxygenase-2 inhibition and renal function. Ann. Intern. Med. 134: 1077–1078

Whelton, A., Fort, J. G., Puma, J. A., Normandin, D., Bello, A. E., Verburg, K. M. (2001) Cyclooxygenase-2-specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. Am. J. Ther. 8: 85–95

Wight, N. J., Gottesdiener, K., Garlick, N. M., Atherton, C. T., Novak, S., Gertz, B. J., Calder, N. A., Cote, J., Wong, P., Dallob, A., Hawkey, C. J. (2001) Rofecoxib, a COX-2 inhibitor, does not inhibit human gastric mucosal prostaglandin production. Gastroenterology 120: 867–873

Wilson, K. T., Fu, S., Ramanujam, K. S., Meltzer, S. J. (1998) Increased expression of inducible nitric oxide synthase and cyclooxygenase-2 in Barrett's oesophagus and associated adenocarcinomas. Cancer Res. 58: 2929–2934

Wockhardt (2002) Wockhardt second quarter 2002 financial results. www.wockhardtin.com/pr_31ajuly2002.htm (accessed 14 April 2003)

Wolf, G., Porth, J., Stahl, R. A. (2000) Acute renal failure associated with rofecoxib. Ann. Intern. Med. 133: 394

Wolfe, F., Anderson, J., Burke, T. A., Arguelles, L. M., Pettitt, D. (2002) Gastroprotective therapy and risk of gastrointestinal ulcers: risk reduction by COX-2 therapy. J. Rheumatol. 29: 467–473

Wong, E., DeLuca, C., Boily, C., Charleson, S., Cromlish, W., Denis, D., Kargman, S., Kennedy, B. P., Ouellet, M., Skorey, K., O'Neill, G. P., Vickers, P. J., Riendeau, D. (1997) Characterization of autocrine inducible prostaglandin H synthase-2 (PGHS-2) in human osteosarcoma cells. Inflamm. Res 46: 51–59

Woolf, E., Fu, I., Matuszewski, B. (1999) Determination of rofecoxib, a cyclooxygenase-2 specific inhibitor, in human plasma using high-performance liquid chromatography with post-column photochemical derivatization and fluorescence detection. J. Chromatogr. B. Biomed. Sci. Appl. 730: 221–227

Woywodt, A., Schwarz, A., Mengel, M., Haller, H., Zeidler, H., Kohler, L. (2001) Nephrotoxicity of selective COX-2 inhibitors. J. Rheumatol. 28: 2133–2135

Wu, A., Wang, Q., Wang, Q., Xu, H., Cheng, M., (2002) Synthesis of new cyclooxygenase-2 inhibitor: rofecoxib. Zhongguo Yaowu Huaxue Zazhi 12: 37–38

Zacher, J., Schattenkirchner, M. (2002) Patient and physician satisfaction with rofecoxib in osteoarthritis: results of a post-marketing surveillance study in primary care in Germany. Curr. Med. Res. Opin. 18: 229–236

Zhao, S. Z., Reynolds, M. W., Lejkowith, J., Whelton, A., Arellano, F. M. (2001) A comparison of renal-related adverse drug reactions between rofecoxib and celecoxib, based on the World Health Organization/Uppsala Monitoring Centre safety database. Clin. Ther. 23: 1478–1491

Ziegler, J. (1999) Early trials probe COX-2 inhibitors' cancer-fighting potential. J. Natl Cancer Inst. 91: 1186–1187